On the synthesis and stereochemistry of some tropanes and piperidines with potential analgesic action

Pascoe, R. Alan

Award date:
1987

Awarding institution:
University of Bath

ON THE SYNTHESIS AND STEREOCHEMISTRY OF SOME TROPANES AND PIPERIDINES WITH POTENTIAL ANALGESIC ACTION

Thesis

Submitted by R. Alan Pascoe B.Pharm., M.P.S.,
for the degree of Doctor of Philosophy
of the University of Bath
1987

This research has been carried out in the School of Pharmacy and Pharmacology under the supervision of Dr. A.F. Casy and Dr. G.H. Dewar

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

To mum and dad,

whose unfailing support

made the completion

of this work possible.

ACKNOWLEDGEMENT

The author wishes to express his grateful thanks to Dr. Alan F. Casy and Dr. George H. Dewar for their initiation, patience, encouragement and helpful advice throughout the course of this work.

To the staff in the Department of Pharmaceutical Chemistry and to his colleagues the author extends thanks for stimulating discussion on many aspects of the work and for their friendship.

Thanks are also due to Mr. Harry R. Hartell and Mr. Dave Wood for skilled ^{13}C- and ^{1}H-NMR spectra.

The author would like to thank Dr. D. Fries of the University of the Pacific, Stockton, California for supplying a sample of (-)-3'-nitrotartranilic acid and for advice on the resolution procedure of (±)-α-1,2-dimethyl-4-phenylpiperidin-4-ol.

He wishes to express his gratitude to Dr. A.E. Jacobson of the National Institute of Health, Bethesda, for pharmacological evaluation of the compounds prepared.

The co-operation of Anne Cowlin for typing the complete manuscript and Mr David Chatterton who assisted greatly in proof-reading is gratefully acknowledged.

Finally, the author gratefully thanks the Science and Engineering Research Council for financial support.

Summary

A brief review of narcotic analgesics, with particular reference to the 4-phenylpiperidine class, is presented in Chapter 1. The chemical and stereochemical features of the 4-phenylpiperidines that ensure high levels of activity are discussed, with emphasis on the conformational and configurational aspects of C-methyl derivatives of the reversed ester of pethidine.

One aspect of the chemistry of the 4-phenylpiperidine analgesics that is highlighted is the effect of meta-hydroxy substitution in the aromatic ring. In 4-phenylpiperidine analgesics with C_4-carbon substituents, such a chemical change enhances activity. However, studies of the phenolic analogues of the prodines and allylprodines (with C_4-oxygen substituents), indicate that a complete loss of activity occurs. Hence, it has been suggested that 4-phenylpiperidines with C_4-carbon substituents associate with opiate receptors in a mode closely analogous to that of morphine (axial-4-aryl conformer), while those with C_4-oxygen substituents interact with opiate receptors in a manner involving an equatorial-4-aryl piperidine chair conformer.

The basis for the synthesis of the compounds described in this thesis is to challenge the proposals on receptor interaction of the 4-phenylpiperidines. To this end, the synthesis of a novel series of potential analgesics based on the 3α-phenolic tropane analogue of pethidine and the preparation of the phenolic α- and β-2-methyl analogues of the reversed ester of pethidine are reported (Chapter

2). The particular interest in these derivatives arises as a result of the nature of the 4-aryl group. In both the 3α-phenolic tropane analogues of pethidine (considered as a rigid piperidine as a result of the fused pyrrolidine ring) and the phenolic α-2-methyl analogue of the reversed ester of pethidine, the 4-aryl group is axial in its preferred orientation and hence can be used to elucidate further information of receptor interaction of these types of compounds.

Chapter 2 also describes limited work on the attempted synthesis of the 3α- and 3β-phenolic tropane analogues of the reversed acetyloxy ester of pethidine. Of particular interest was the 3α-analogue, with an axially orientated aryl moiety.

The resolution of (±)-α-1,2-dimethyl-4-phenylpiperidin-4-ol is reported, so as to provide further information on the analgesic potency of optically active forms of chiral diastereoisomers in the 4-phenylpiperidine class of analgesics.

Finally, the pharmacological results of these compounds, available at the time of writing this thesis, are reported and discussed.

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Historical Introduction

Prior to the advent of modern synthetic chemistry, natural products provided the only means of drug treatment. Of all the herbal remedies that were available, opium was probably the most effective drug of them all.

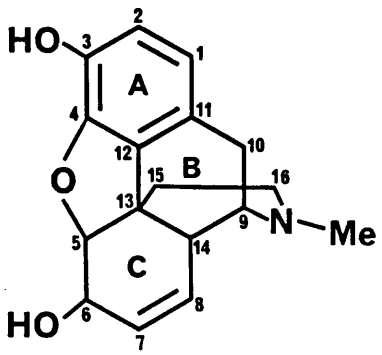
Opium has been used as a drug at least since the classical times, not only because it deadens pain but because it also produces a sense of well-being in the user. In 1803, morphine (1) was isolated from opium by a German pharmacist and by the middle of the 19th century the use of pure morphine, rather than crude opium preparations, had spread widely.

Apart from its pain relieving properties, morphine also affects many of the vital centres in the brain. One notable feature is the development of tolerance with repeated use, resulting in the user becoming emotionally and physically dependent on the drug. The widespread use of morphine resulted in a dramatic increase in addiction, and hence the drug was the cause of a significant social problem. This resulted in the search for non-addictive synthetic (and semi-synthetic) opiates, lacking the undesirable effects of morphine.

1.2 Morphine and its Derivatives

Morphine (1), the chief alkaloid obtained from opium, Papaver somniferum, was isolated by the German pharmacist Sertuner. Its structure, originally proposed by Gulland and Robinson in 1923[1,2], was not confirmed until its total synthesis in 1952 by Gates and Tschudi[3].

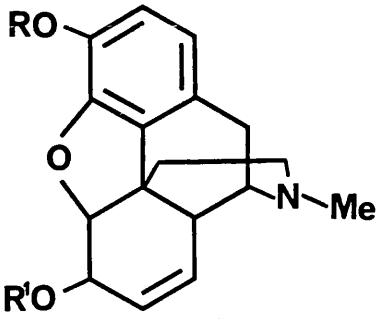
Used as an agent against severe and chronic pain, morphine may be regarded as the prototype among the analgesic drugs. However, its multiple side effects, such as respiratory depression, gastro-intestinal disturbances and the development of tolerance leading to addiction, have led to much modification of the morphine molecule in an effort to produce the ideal centrally-acting analgesic.



(1)

Early modification of morphine, in an attempt to produce analgesics superior to the natural product, involved derivatisation of the 3- and 6- hydroxy groups. Acetylation of both hydroxy groups yielded

the analgetically potent and highly addicting diacetylmorphine (Heroin, 2), whereas etherification of the phenolic hydroxy group lowered the analgetic potency, as illustrated by codeine (3) and pholcodine (4).

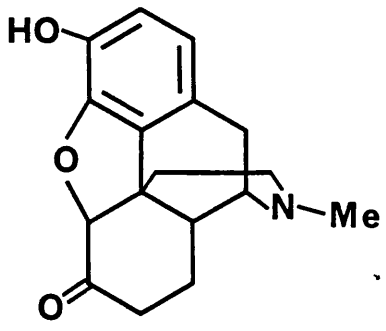


(2) $R=R^1=COCH_3$

(3) $R=Me$, $R^1=H$

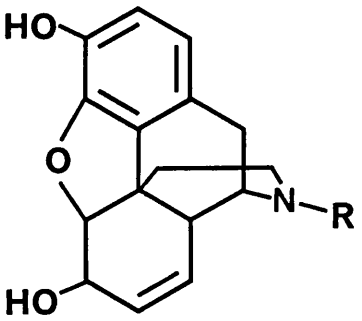
(4) $R=CH_2CH_2-N\langle O \rangle$, $R^1=H$

Other modifications involved chemical transformations within ring C of morphine which generated several drugs having morphine-like activities, although these derivatives offer no real advantage over morphine itself. One example is dihydromorphinone (5).



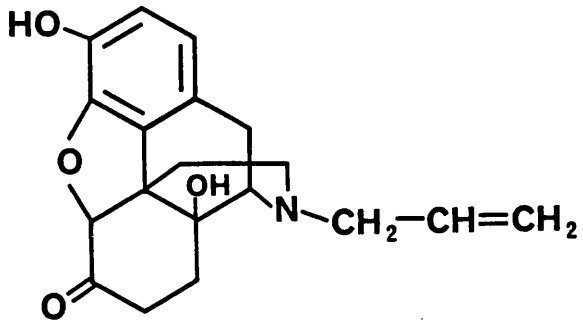
(5)

Alteration of groups on the nitrogen of the morphine nucleus has a major effect on both the quantitative and qualitative activity of morphine. The N-phenethyl analogue (6), is more potent than morphine, but with qualitatively similar activity[4]. Substitution by groups such as allyl, dimethylallyl and cyclopropylmethyl impart antagonist activity to morphine. The N-allyl compound (Nalorphine, 7) was one of the first compounds recognised as a morphine antagonist[5], and has been used as an antidote in morphine poisoning[6]. Although nalorphine lacks analgesic properties in laboratory animals, in humans it shows potent, essentially non-addicting analgesic effects. This observation has led to the development of several clinically useful analgesics based on morphine antagonists[7]. One morphine antagonist that has attracted much interest is the N-allyl analogue of oxymorphone (Naloxone, 8), which is considered to be an almost pure antagonist as it does not exhibit any analgesic activity[8].



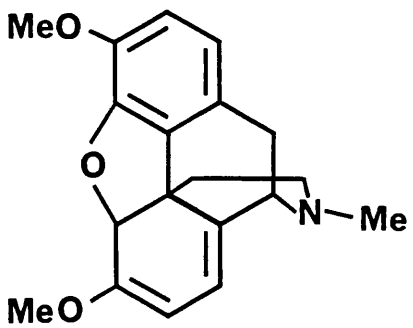
(6) R=CH_2CH_2Ph

(7) R=CH_2-CH=CH_2

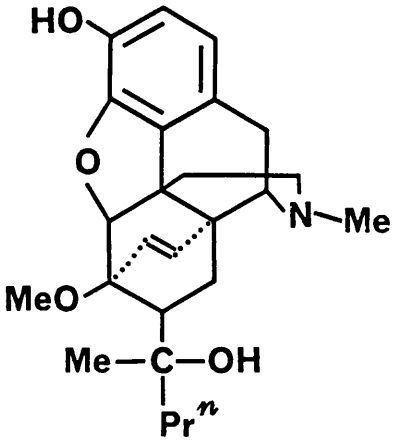


(8)

Bentley and co-workers utilized the medically useless alkaloid thebaine (9) to produce a series of morphine analogues called the oripavines[9]. Thus, exploitation of the diene component of thebaine *via* Diels Alder condensations with a variety of dienophiles, gave rise to ketonic adducts with activities comparable to those of morphine, while certain tertiary alcohols derived from Grignard reactions on these ketonic adducts were shown to have very high levels of activity. One such compound, etorphine (10), has an activity 1,000-10,000 times that of morphine in a variety of animal species[10].



(9)



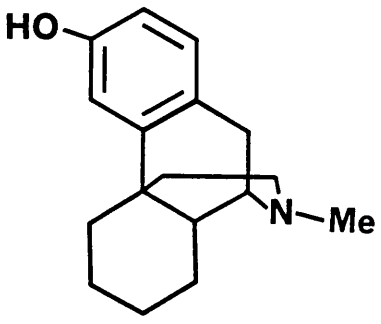
(10)

1.3 Synthetic Centrally-Acting Analgesics

Research in the field of synthetic, centrally-acting analgesics has concentrated on modification of the morphine structure in an attempt to extract the pharmacophore necessary for activity. Although not in chronological order of development, the following sections attempt to illustrate how a continual reduction in the size of the morphine molecule has generated various groups of drugs with analgesic properties. Though these analgesics vary in structural characteristics, they can all be related to the prototype, morphine (see Fig.1).

1.3.1 The Morphinans

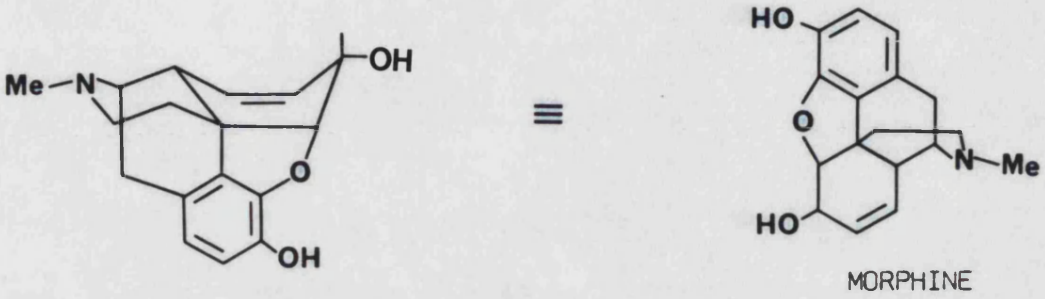
The morphinans, investigated by Grewe[11,12] in his total synthesis of morphine, bear the closest structural similarity to the natural product, as they contain the complete carbon-nitrogen skeleton (see Fig.1,a). Among the various derivatives within this group, racemorphan (11) was the first clinically valuable agent, with twice the activity of morphine[13]. Resolution of racemorphan, and subsequent pharmacological testing of each enantiomer, revealed that analgesic potency resided almost completely in the laevo isomer, levorphanol[14].



(11)

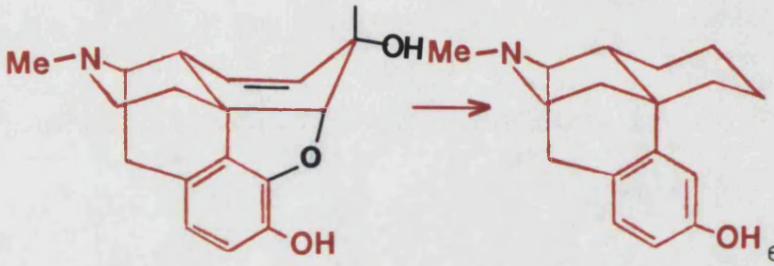
Figure 1

Structural elements of (a) the morphinans, (b) the benzomorphans, (c) the phenylpiperidines and (d) the diphenylpropylamines as they relate to morphine



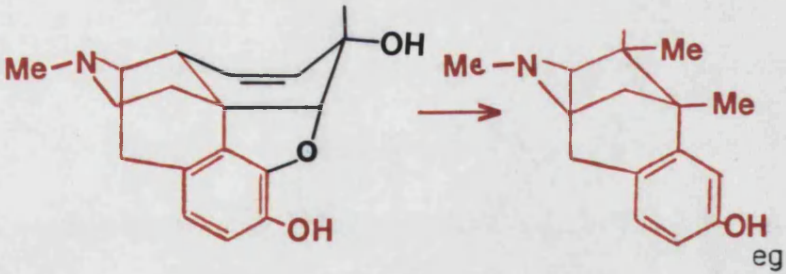
MORPHINE

(a)



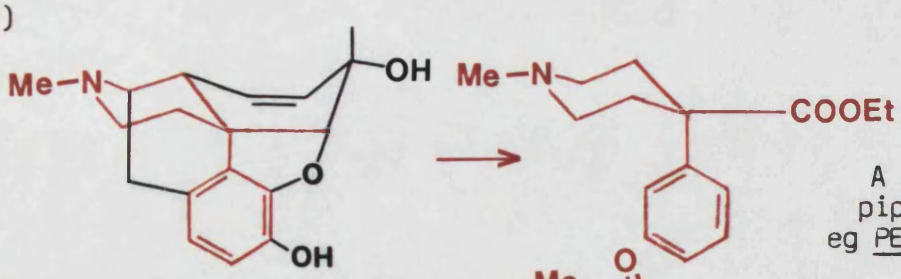
A morphinan
eg RACEMORPHAN

(b)



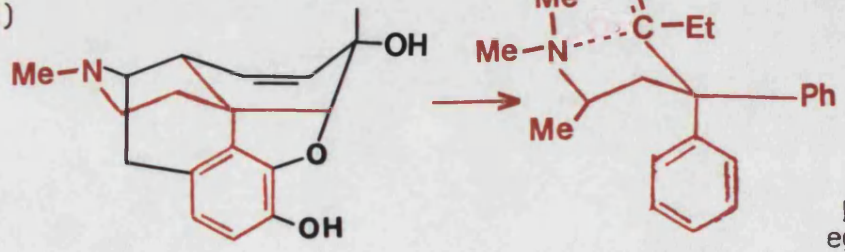
A benzo-
morphan
eg α-METAZOCINE

(c)



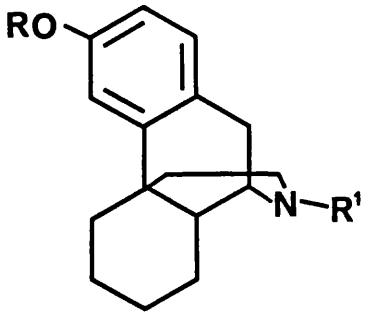
A phenyl-
piperidine
eg PETHIDINE

(d)



A diphenyl-
propylamine
eg METHADONE

Structure-activity relationships among the morphinans closely mirror those of morphine, although few changes have resulted in useful drugs. Two clinically useful agents are worthy of note: levallorphan (12), the N-allyl analogue of levorphanol, is an analgesic antagonist with five times the potency of nalorphine[15], whilst dextromethorphan (13), the O-methyl ether of the dextro isomer of racemorphan, has found extensive use as a non-addictive anti-tussive agent.



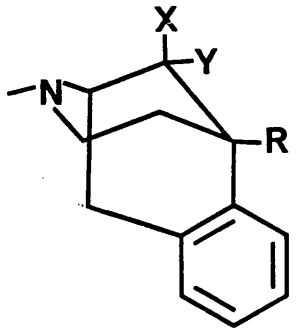
(12) R=H, R^1=$CH_2CH{=}CH_2$

(13) R=R^1=Me

1.3.2 The 6,7-Benzomorphans

Simplification of the morphine structure was carried a step further by May and associates in 1954 with the advent of the 6,7-benzomorphans[16]. In this set of compounds ring C of morphine has been replaced by methyl or other alkyl substituents at C-5 and C-9, a chemical change which confers an additional geometrical isomerism across ring B (see Fig.1,b). Termed alpha (α-, cis 5,9-dialkyl, 14) and beta (β-, trans 5,9-dialkyl, 15) benzomorphans, greater

analgesic activity, dependence liability and toxicity is associated with the β-series, and, additionally, agonist activity resides mainly in the laevo isomers[17].



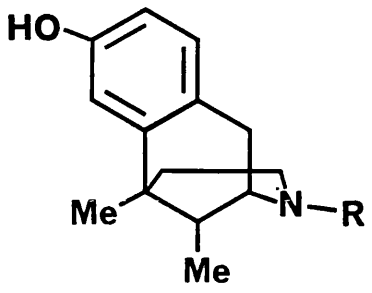
(14) α- : X=H, Y=R^1

(15) β- : X=R^1, Y=H

Clinically important 6,7-benzomorphan derivatives include phenazocine (16; N-phenethylnorbenzomorphan), with 3-5 times the activity of morphine in man but a lower dependence liability[18], and pentazocine (17), the N-dimethylallylnorbenzomorphan derivative[19,20]. Although a feeble antagonist of morphine, pentazocine is an effective analgesic in man. It was marketed as an analgesic with low addicitive liability (as 'Fortral'), but clinical experience has disproved this latter aspect, so that it is now classified as a controlled drug.

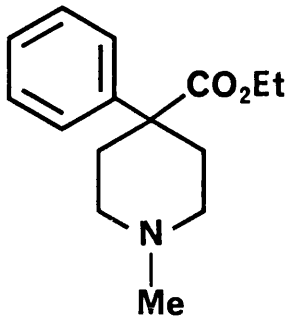
(16) R=CH_2CH_2Ph

(17) R=$CH_2CH{=}CMe_2$



1.3.3 The 4- Phenylpiperidines

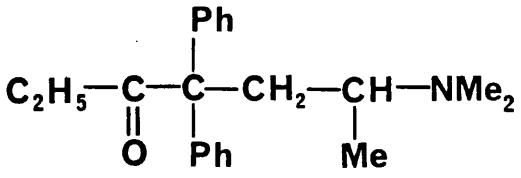
The serendipitous discovery of pethidine, in 1939 by Eisleb and Schaumann[21], represents further simplification of the morphine molecule. Pethidine (18), the parent compound of the 4-phenylpiperidine analgesics, was originally synthesised as a potential antispasmodic agent. Its analgesic properties were observed in the course of clinical trials, and, with hind-sight, its structure can be assigned to a portion of the morphine molecule (see Fig.1,c). A full consideration of the chemistry and stereochemistry of the 4-phenylpiperidines and related compounds is given in section 1.4.



(18)

1.3.4 Diphenylpropylamine Analgesics

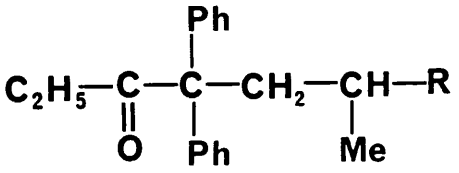
The discovery of such a simple narcotic agent as pethidine influenced the direction of research and resulted in the ultimate simplification of the morphine structure in the preparation of the acyclic analgesic, methadone (19)[22,23]. This acyclic analgesic, a 3,3-diphenylpropylamine derivative, was one of the early non-fused ring analgesics recognised. A possible conformational relationship of methadone to morphine has been postulated (see Fig.1,d).

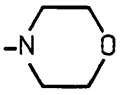


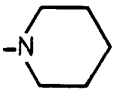
(19)

Clinically similar to morphine, methadone has the advantage that it sustains addiction at one quarter the dose of morphine, and withdrawal effects, both physical and emotional, are less severe.

Hence, its major use is in the maintenance of narcotic dependent subjects[24]. Structural analogues of methadone generally show reduced activity or are inactive[25]. Variations about the nitrogen atom of methadone that have produced clinically useful drugs include use of the morpholino group, as in phenadoxone (20)[26], and the piperidino group, as in dipipanone (21)[27].



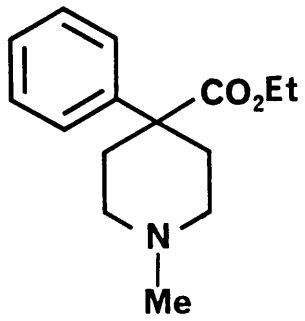
(20) R= 

(21) R= 

1.4 4-Phenylpiperidine Analgesics and Related Compounds

1.4.1 Introduction

The 4-phenylpiperidine type of analgesics are historically the oldest synthetic group. Pethidine (18), the parent compound of this group, is one of the most widely accepted substitutes for morphine, and was first introduced into clinical practice by Eisleb and Schaumann in 1939[21].



(18)

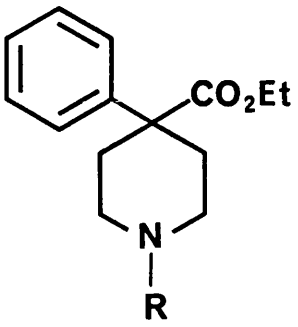
Pethidine has about one fifth to one eighth the potency of morphine in man[28], and is useful in the control of mild to moderate pain. However, it shows little advantage over the natural product, except that it has a lower level of toxicity and shorter duration of action. Clinically, pethidine has many uses, although its major use is in the control of labour pain[29], a clinical application which has attracted some criticism[30]. Extensive research into synthetic modifications of pethidine has been undertaken with the aim of producing an ideal analgesic, and also to investigate the structure-activity relationships that apply among the 4-phenylpiperidines.

1.4.2 Synthetic Modifications of Pethidine

1.4.2.1 Variation of the Nitrogen Substituent

Following the observation made by Perrine and Eddy in 1956 that N-phenethylnorpethidine (Pheneridine, 22) had a potency twice that of pethidine in mice[31], a full investigation into other N-substituted norpethidines was undertaken. It has become apparent that the potency of analogues in the 4-phenylpiperidine series depends heavily upon the nature of the nitrogen substituent. Substitution on the phenyl of pheneridine with groups such as amino and methoxy is consistent with good potency, as is hydroxylation in the side chain. Varying the length of the side chain alkyl also dramatically effects potency. Activity rises from N-benzyl- (0.25 times as potent as pethidine) to N-phenylpropylnorpethidine (13 times as potent as pethidine), and then decreases on further extension of the alkyl chain[32]. Replacement of the side chain aryl by pyridyl enhances activity[33], whilst the dioxolane group in that position gives a compound with the same potency as the parent ester[34].

N-substituted analogues of pethidine in clinical use include phenoperidine[30] (Operidine, 23), the secondary alcohol obtained from the reduction of the Mannich base derived from norpethidine and acetophenone, with a potency of 150 times pethidine[35,36]; anileridine (Leritine, 24), the N-para aminophenethyl analogue of pethidine, with 2-3 times the potency of the parent[37,38]; and piminodine (Alvodine, 25), possessing an N-substituent containing a secondary amino group between the alkyl and aryl function, a drug 100 times more potent than pethidine[39].



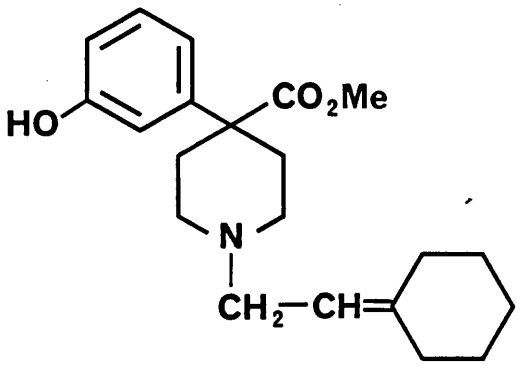
(22) $R=CH_2CH_2Ph$

(23) $R=CH_2CH_2CHOHPh$

(24) $R=CH_2CH_2$-C$_6$H$_4$-NH_2

(25) $R=CH_2CH_2CH_2$-NH-Ph

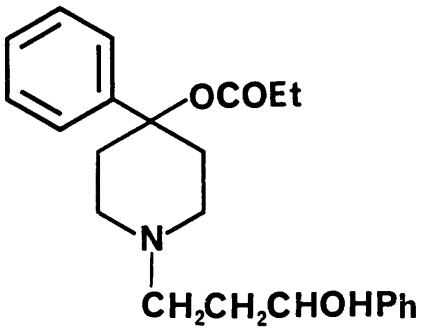
Research aimed at producing a narcotic antagonist based on 4-phenylpiperidines, involving a change of the N-substitutent, has not produced an effective agent. Linking the nitrogen atom to groups such as allyl or cyclopropylmethyl, modifications which produce antagonists in the morphine and benzomorphan series, have led to agents having no power to block opiate receptors[40]. However, partial success in producing 4-phenylpiperidine antagonists has been achieved: compound (26), based on bemidone, is reported to have one third the activity of nalorphine against morphine[41].



(26)

1.4.2.2 The C-4 Oxygen Function

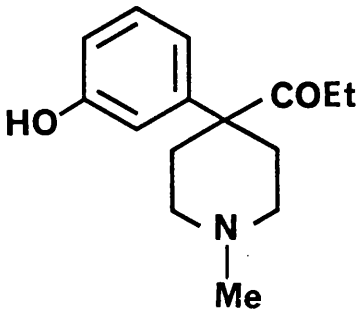
Investigations into the variation of the C-4 oxygen function of pethidine, and its effect on analgesic potency, were carried out soon after the drug was introduced into clinical practice. The carbethoxy group (CO_2Et) is considered to be of optimal size for analgesic activity[42], and its replacement by carbomethoxy[43], or higher alkyl esters, decreases activity[35,36]. However, in 1943 it was reported that the replacement of 4-carbethoxy by 4-propionyloxy (OCOEt) enhanced potency by a factor of 20[43,44]. This group of analgesics, the so-called reversed esters of pethidine, showed high levels of potency irrespective of the nature of the nitrogen substituent. Further increases in potency were observed within this series when nitrogen substituents known to confer high levels of activity in the pethidines were introduced. The reduced Mannich product (27) is one of the most potent phenylpiperidines, displaying activity some 3,200 times that of pethidine in rats[45].



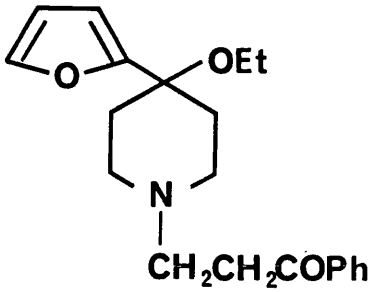
(27)

The ease of their synthetic accessibility, together with their enhanced levels of activity, have resulted in much of the research of the 4-phenylpiperidine type of analgesics being based on the reversed esters. Studies on the effect of variation of the 4-aryl group, and investigations into the structure-activity relationship of various C-alkyl analogues, are considered in sections 1.4.2.3 and 1.4.2.4 respectively.

Other changes at the C-4 oxygen position include the replacement of the ester by ketonic functions and alkyl ethers. Ketobemidone (28) possesses a 4-propionyl group together with a 4-m-hydroxyphenyl group, and has 10 times the potency of pethidine[46]. The 4-ethoxy-4-(2'-furyl) analogue (29) of pethidine has 2.5 times the activity of the parent[47].



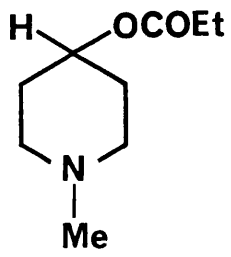
(28)



(29)

1.4.2.3 Variation of the 4-Aryl Group

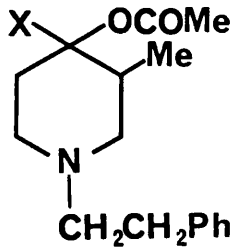
Much of the work investigating a change in the nature of the 4-aryl group of the 4-phenylpiperidines, and its effect on analgesic potency, has utilized the synthetically accessible reversed esters. Complete removal of the 4-phenyl results in a dramatic fall in potency (see 30)[48,49], whilst its replacement by larger groups such as naphthyl[50], or non-aromatic groups capable of donating π electrons, such as ethynyl[51], abolishes activity completely. Isosteric replacement of phenyl by groups such as furyl, pyridyl and thienyl are also disadvantageous in terms of potency (see 31)[47,50,52].



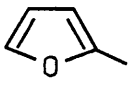
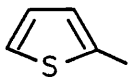
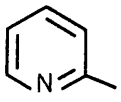
(30)

(30): ED_{50} : 20.2 mg/Kg SC (mice HP)

CODEINE ED_{50} : 7.5 mg/Kg SC (mice HP)

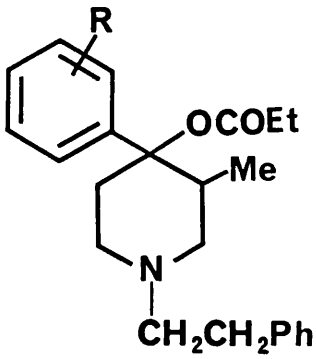


(31)

X	Activity[47,50]
	Inactive
	63
	30

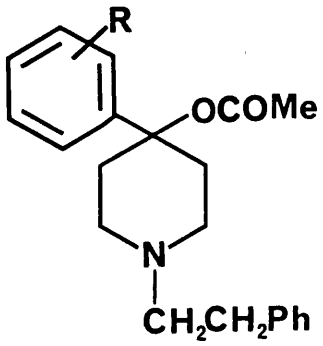
MORPHINE: 100

The introduction of substituents into the aromatic ring, such as methyl (32) and methoxy (33) has been reported, although in most cases these analogues are less potent than the parent compounds. No correlation between potency and position of substitution can be observed, although para substitution usually results in the greatest, and ortho the least, fall in activity.



(32)

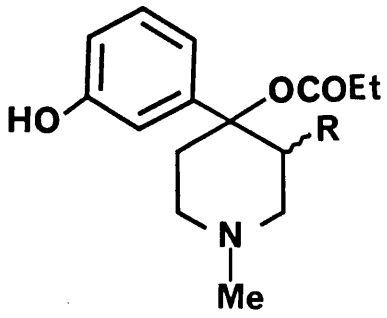
	Activity[53]
R = H	4.3
R = o-Me	2.6
R = m-Me	0.4
R = p-Me	0.2
MORPHINE	1.0



(33)

	Activity[54,55]
R = H	5.7
R = o-OMe	3.0
R = m-OMe	0.5
MORPHINE	1.0

Studies on the effect of other aromatic substituents are lacking although the influence of hydroxylation in the aryl ring has been investigated. Hydroxylation of the 4-phenyl group, a situation which increases analgesic potency in the fused ring systems, generally leads to a marked reduction or complete loss of activity in many 4-phenylpiperidine analgesics. Thus, meta-phenolic analogues (34), (35) and (36) of the reversed ester of pethidine, α- and β- prodine and α- and β- allylprodine respectively, have been shown to be inactive in in vitro and antinociceptive tests for analgesia[56,57].

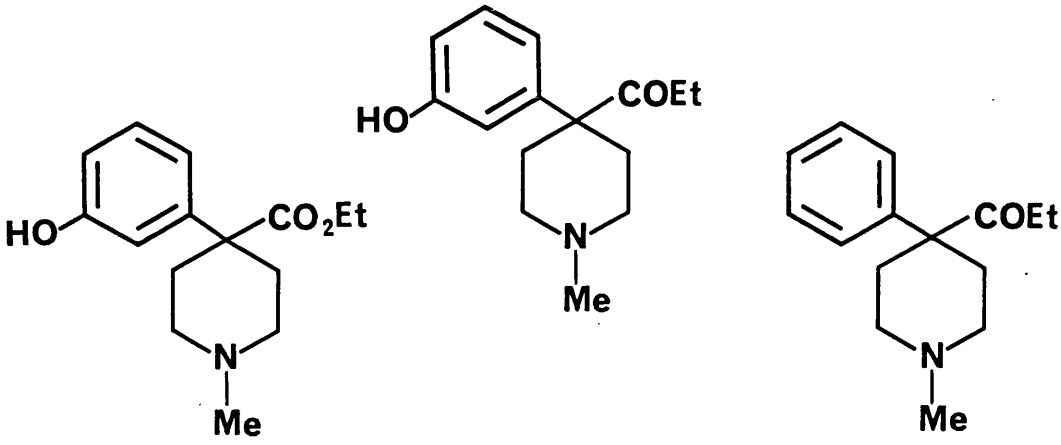


(34) R=H

(35) R=Me

(36) R=$CH_2CH=CH_2$

However, the introduction of a meta-phenolic hydroxyl into pethidine, as in bemidone (37), elevates potency by a factor of 1.5, while ketobemidone (28), is approximately 20 times more potent than the corresponding non-phenolic analogue (38)[58].



(37) (28) (38)

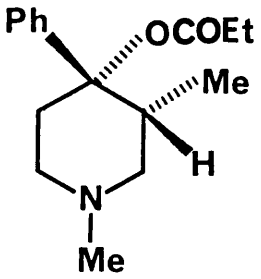
1.4.2.4 Alkylation of the Piperidine Ring

Investigation into the effect of alkylation of the heterocyclic ring of the 4-phenylpiperidines has mainly been confined to the reversed esters. This can be attributed to the versatility of the 4-aryl-4-piperidinol synthesis, and the high levels of activity associated with the reversed esters. Following the reports in the late 1940s on the 3-methyl analogues of the reversed esters of pethidine[59], many 3-alkyl derivatives, and all possible mono- and di-C-methyl derivatives, of the reversed esters have been described.

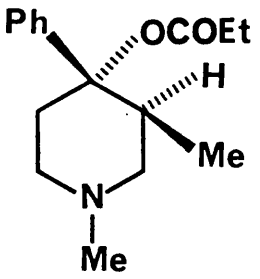
A. The Isomeric 3-Alkyl Analogues of the Reversed Ester of Pethidine

The isomeric nature of the 3-methyl derivatives of the reversed ester of pethidine were first studied by Ziering et al. in 1947[60].

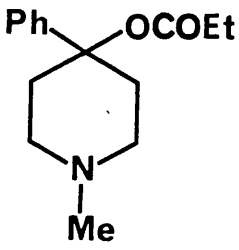
They reported a potency difference between the two diastereoisomers, examined as racemates. Alpha-prodine (39), the major component, was reported to have a potency equivalent to morphine, whereas the minor component, beta-prodine (40), was five times as active as the standard agent[59]. Many reports since 1947 have confirmed these original findings and, in addition, beta-prodine has been shown to be five times as potent as the parent desmethyl compound (41)[61], a potency level not shown by the corresponding α-isomer.



(39)



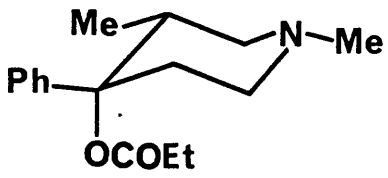
(40)



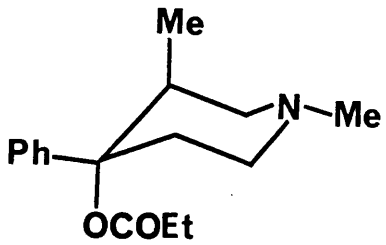
(41)

	(39)	(40)	(41)
ED_{50} mg/Kg	0.92	0.18	0.85

The original configurations assigned to alpha- and beta-prodine remained controversial until they were established by X-ray crystallographic analyses[62], and substantiated by ^{1}H- and ^{13}C-n.m.r. studies[63,64,65,66]. The assignments are trans 3-methyl/ 4-phenyl for α-prodine (39a) and cis 3-methyl/4-phenyl for β-prodine (40a). The corresponding IUPAC nomenclature is α: c-3-Me, r-4-OCOEt; β: t-3-Me, r-4-OCOEt. Both diastereoisomers are considered to exist in the equatorial 4-phenyl chair conformation.



(39a)



(40a)

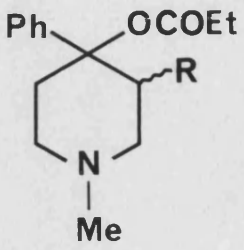
{These structures are meant only to express relative stereochemistry at this stage. Details of absolute stereochemistry are presented on page 26.}

However, it is now accepted that the case of the 3-methyl substituent is unique, and with larger alkyl groups those compounds with a trans 3-alkyl/4-phenyl configuration (the α-isomers) are more potent than their corresponding cis 3-alkyl/4-phenyl analogues[67] (see Table 1). From this data it appears that drug-receptor interaction is enhanced by α-ethyl and impeded by α-n-propyl and α-n-butyl, while all β-substituents except methyl have a detrimental influence.

Receptor affinities measured by determining the concentration of the 3-alkylated ester to displace 50% of specifically bound [^{3}H] dihydromorphine from rat brain homogenates have confirmed the higher affinity of β- over α- (42, R=Me, Table 1) and α- over β- (42, R=Et and n-hexyl, Table 1), and the results were found to correlate well with analgesic potency[68].

Table 1

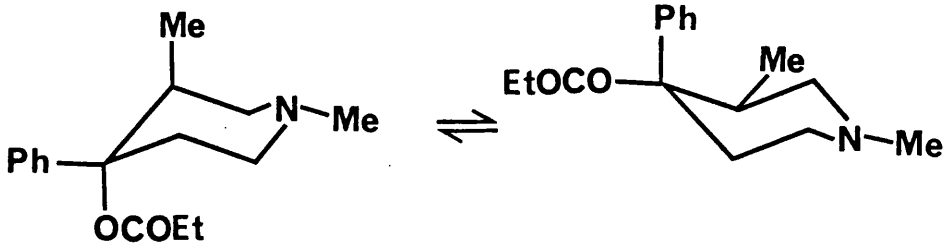
Analgesic Activity (Hot Plate ED_{50} mg/Kg SC in mice) of Some Reversed Esters of Pethidine[67]



(42)

R	α- (t-3R/4-Ph)	β- (c-3R/4-Ph)
H	0.85	0.85
Me	0.92	0.18
Et	0.4	3.5
Pr^n	2.0	14.7
Bu^n	54.7	12.8
$C_6H_{13}{}^n$	inactive at 80	54.4

The influence of a β-3-methyl group may be achieved directly through interaction with a binding site on the receptor specific for axial methyl. However, longer hydrocarbon groups of the same axial orientation are not accommodated at this site. An alternative explanation, however, is that a β-3-methyl group has an indirect influence on ligand-receptor association by facilitating a rise in the population of reversed ester conformations that bind more effectively than the equatorial 4-phenyl chairs favoured for unsubstituted and 3α-substituted derivatives. Thus, the axial 4-phenyl chair (43) may have greater receptor affinity than the corresponding equatorial 4-phenyl chair analogue (40a).



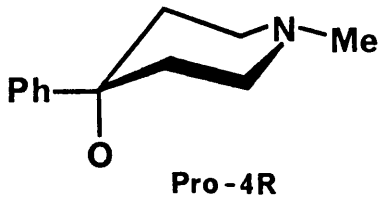
(40a) (43)

Following the establishment of the conformation and relative configuration of alpha- and beta-prodine, an investigation into the analgesic potency of the two optical forms of each chiral diastereoisomer was necessary to complete a comprehensive study of the structure-activity relationships of the prodine-type reversed esters. This involved separation of the two chiral diastereoisomers into antipodal forms, elucidation of the absolute configuration of each enantiomer, and the assessment of each

enantiomers' analgesic potency. Portoghese and co-workers[69] succeeded in achieving these aims, the findings of which are given below. For this analysis, they considered the 4-phenylpiperidine reversed esters to exist in favourable equatorial 4-phenyl chair conformations, and by using biochemical nomenclature[70], differentiated between the two sides of the piperidine molecule. One side was termed pro-chiral-4S (Pro-4S) and the other pro-chiral-4R (Pro-4R; see 44). In the unsubstituted parent ester (41) C-4 is symmetrical; substitution of a methyl (or other alkyl)

Pro-4S

Partial formula

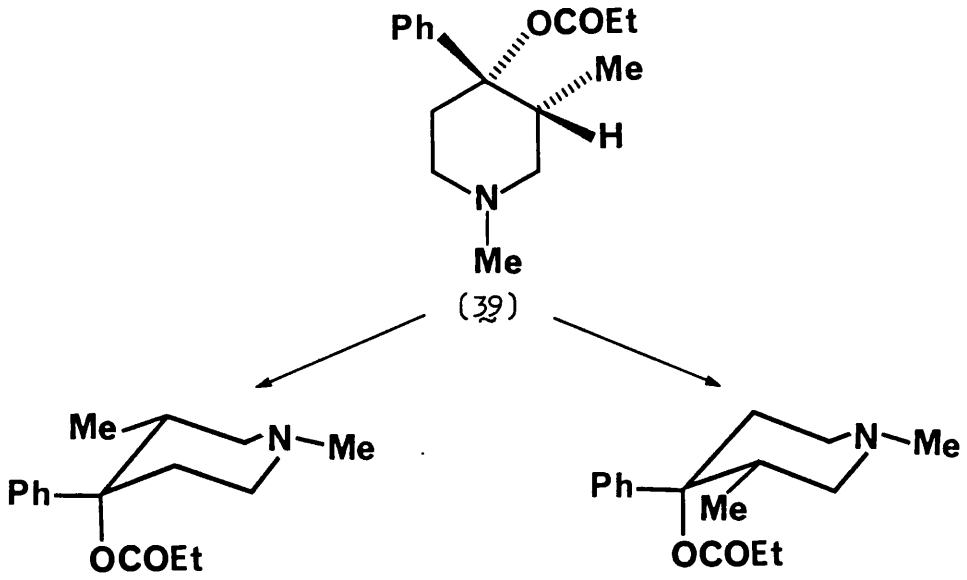


Pro-4R

(44)

group on the Pro-4S side gives C-4 an S configuration (using the Cahn-Ingold-Prelog convention[71]), whilst substitution on the Pro-4R side gives C-4 an R configuration.

Considering the two antipodal forms of alpha-prodine (39), with an equatorial 3-methyl substituent, more activity was found to reside with the 3R,4S enantiomer (39a) than the corresponding 3S,4R enantiomer (39b)[69].

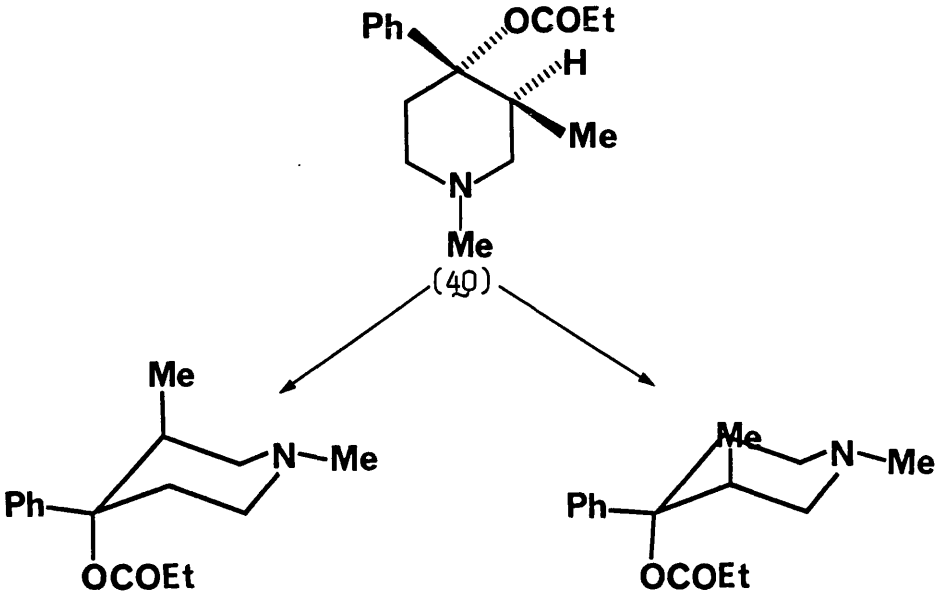


(39)

	3R,4S	3S,4R
	(39a)	(39b)
ED_{50} mg/Kg	0.91	22.4

These findings seem to suggest that the opiate receptor discriminates against the Pro-4S side of the molecule. Thus, if the Pro-4R side of the molecule is presented to the opiate receptor, equatorial 3-methyl substituents located on this side hinder drug receptor interaction, whereas equatorial 3-methyl groups on the Pro-4S side do not affect this interaction. This analysis is further substantiated by studies on other antipodal forms of 3-α-alkyl analogues. One example to illustrate this is the 3-α-n-propyl derivatives of the reversed ester of pethidine: the 3R,4S enantiomer (ED_{50} = 1.0mg/Kg) has a higher level of potency than the corresponding 3S,4R podal form (ED_{50} = 25.2mg/Kg)[72,73].

A similar study of the two antipodal forms of β-prodine (40), in which the 3-methyl substituent has an axial orientation, revealed that greater analgesic potency resided with the 3S,4S antipode (40a) compared to the 3R,4R isomer (40b)[69].



	(+)-3S,4S (40a)	(-)-3R,4R (40b)
ED_{50} mg/Kg	0.25	3.3

Hence, with an equatorial 4-phenyl chair conformation, axial 3-methyl substitution on the Pro-4S side is preferential for high levels of activity and, in addition, such axial 3-methyl substitution has an active role to play in opiate-receptor interaction. This is illustrated by comparison of the analgesic activities of 3R,4S-α-3-methyl and 3S,4S-β-3-methyl analogues of reversed ester of pethidine.

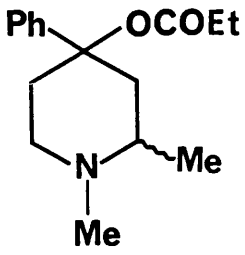
B. Conformation, Relative Configuration and Analgesic Potency of Other C-Methyl Analogues of Reversed Esters of Pethidine

Following the original investigations of the 3-methyl analogues of the reversed ester of pethidine (alpha- and beta- prodine), studies of other mono- and di-C-methyl analogues have been reported. These include 2-methyl, 2,6-, 2,5-, 2,3- and 3,5- dimethyl derivatives. As part of the comprehensive study on the structure-activity relationship of the 4-phenylpiperidine analgesics, it was necessary to deduce the preferred conformation and relative configuration of the members of each isomeric set. The findings of these studies are given in this section. An analysis of the two optical forms of each diastereoisomer, which includes the elucidation of the absolute configuration of each enantiomer, and the assessment of the analgesic potency of each podal form, is discussed in section 1.4.2.4(C).

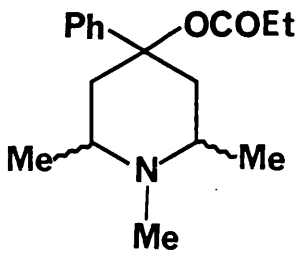
{To simplify the subsequent formulae representing relative or absolute configuration, methyl groups are denoted by a single line defining position and orientation (axial or equatorial) of substitution.}

a) The 2-methyl and the 2,6-dimethyl analogues of the reversed ester of pethidine

Studies on the 2-methyl (45) and the 2,6-dimethyl (46) analogues of the reversed esters of pethidine were initiated by Harper et al.[74] in 1960.

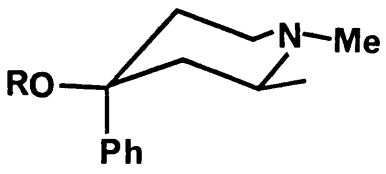


(45)

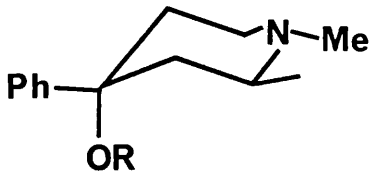


(46)

The stereochemical features of the two 2-methyl isomers were assigned by analysis of their corresponding precursor alcohols. The original assignments of α-(c-2-Me, r-4-OH; 45a, R=H) and β-(t-2-Me, r-4-OH; 45b, R=H) based on chemical reactivity and infra-red analyses, were later confirmed by ^{1}H-[75] and ^{13}C-n.m.r. studies[66].



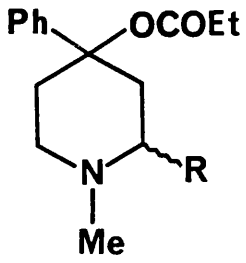
(45a)



(45b)

It should be noted that whilst the β-isomer exists in an equatorial 4-phenyl chair conformation, an axial 4-phenyl chair is preferred for the α-isomer. Assessment of the analgesic potency of the propionate esters of the two racemic diastereoisomers revealed that

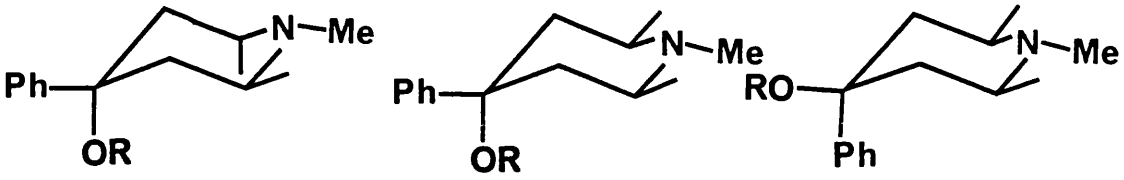
both isomers showed the same level of potency and, in addition, were more potent than the standard agent pethidine but less active than the desmethyl parent ester (see 47)[75].



	R	ED_{50} mg/Kg mice HP
	H	0.85
α:	c-2-Me, r-4-OCOEt	1.32
β:	t-2-Me, r-4-OCOEt	1.37
	pethidine	4.7

(47)

Similar studies on the 1,2,6-trimethyl derivatives (46) revealed that three possible diastereoisomers existed, one chiral (46a, R=H) and two achiral (46b and 46c, R=H). The preferred conformation and relative configuration of each isomer was established by X-ray crystallographic analysis of the precursor piperidinol[76] (46a, 46b, 46c, R=H). The results were further substantiated by ^{1}H-n.m.r. studies of the corresponding acetate esters[77] (46a, 46b, 46c, R=COMe).

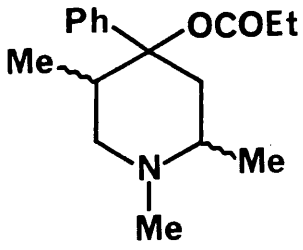


(46a) (46b) (46c)

Studies of analgesic potency of the three diastereoisomers within the set revealed that the two achiral molecules were inactive (46b, R=COMe; 46c, R=COMe) whilst the chiral species (46a, R=COMe) was active. The ED_{50} of 46a (R=COMe) was found to be 2.0 mg/Kg compared with pethidine at 4.7 mg/Kg (mice, hot plate test)[77].

b) The 2,5-dimethyl analogues of the reversed ester of pethidine (The promedols)

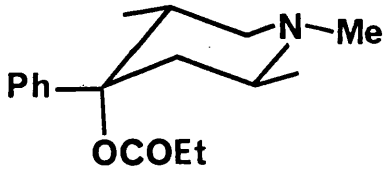
The 2,5-dimethyl analogues of the reversed esters of pethidine (48) were first investigated by Nazarov et al.[78] in 1948. They succeeded in isolating three (α-, β- and γ-) of the four possible diastereoisomers, and assessed each for analgesic activity. The fourth isomer, δ-, was later reported by Russian workers in 1959[79].



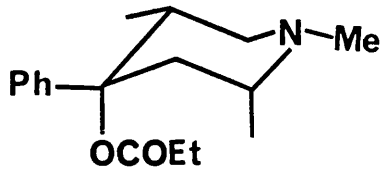
	Activity[80,81]
α- :	8
β- :	4
γ- :	2
δ- :	4-6
Morphine:	1

(48)

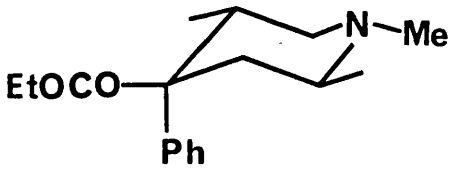
The stereochemical characteristics of each diastereoisomer were established by Casy et al.,[81,82]. Studies of the precursor piperidinols by chemical reactivity and ^{1}H-n.m.r. spectroscopy enabled the relative configuration and preferred conformation of the α-, β- and γ- promedols to be deduced. These results were further substantiated by ^{13}C-n.m.r.[83] and X-ray crystallographic studies[84]. γ-(t-2-Me, c-5-Me, r-4-OCOEt; 48a) and β-(c-2-Me, c-5-Me, r-4-OCOEt; 48b) promedols were shown to exist in favourable equatorial 4-phenyl chair conformations, whilst the α-isomer (c-2-Me, t-5-Me, r-4-OCOEt) exists as an axial 4-phenyl chair (48c). The configuration of the δ-isomer has not been established but by elimination must be t-2-Me, t-5-Me, r-4-OCOEt (48d).



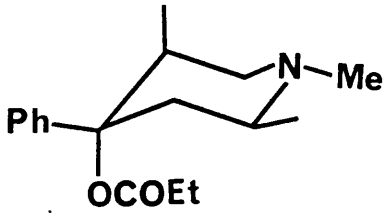
(48a)



(48b)



(48c)

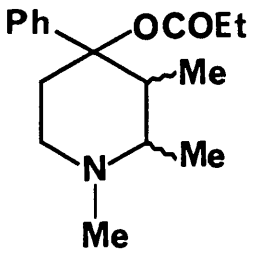


(48d)

c) The 2,3-dimethyl analogues of the reversed esters of pethidine

First reported in 1961[85], the four possible diastereoisomers of the isomeric 1,2,3-trimethyl-4-phenyl-4-piperidinols were isolated by Mastryukov et al.[86]. They analysed each racemic diastereoisomer for analgesic potency (as the propionate ester) and showed that, whilst the α- and γ- isomers were analgetically potent, the β- and δ- diastereoisomers were inactive (see 49).

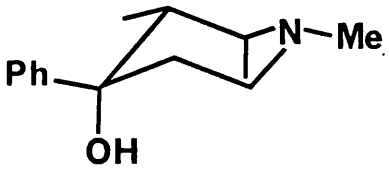
The stereochemical properties of these four diastereoisomers, investigated as the precursor alcohols, was undertaken by Casy et al.[87] on the basis of ^{1}H- and ^{13}C-n.m.r. studies.



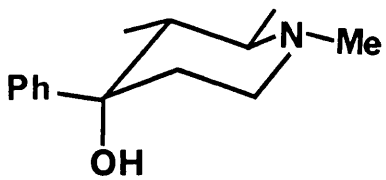
	Activity
α- :	1
β- :	inactive
γ- :	30
δ- :	inactive
Morphine:	1

(49)

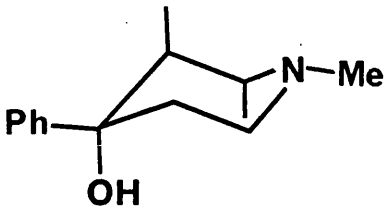
All four diastereoisomers were shown to exist in a favourable 4-phenyl chair conformation and the relative configuration of each isomer was established as α- (c-2-Me, c-3-Me, r-4-OH; 49a), β- (t-2-Me, c-3-Me, r-4-OH; 49b), γ- (c-2-Me, t-3-Me, r-4-OH; 49c) and δ- (t-2-Me, t-3-Me, r-4-OH; 49d).



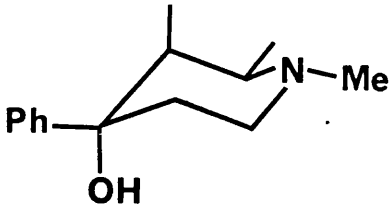
(49a)



(49b)



(49c)



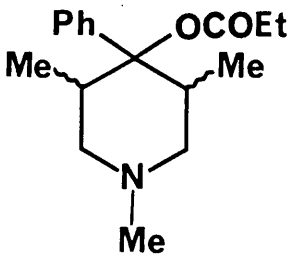
(49d)

Further studies of the potency of the α- and γ-diastereoisomers has been undertaken and compared with that of the parent desmethyl ester. The γ- isomer was shown to have four times the activity of the parent, whilst the α-isomer was only 0.25 times as active[88].

d) The 3,5-dimethyl analogues of the reversed esters of pethidine

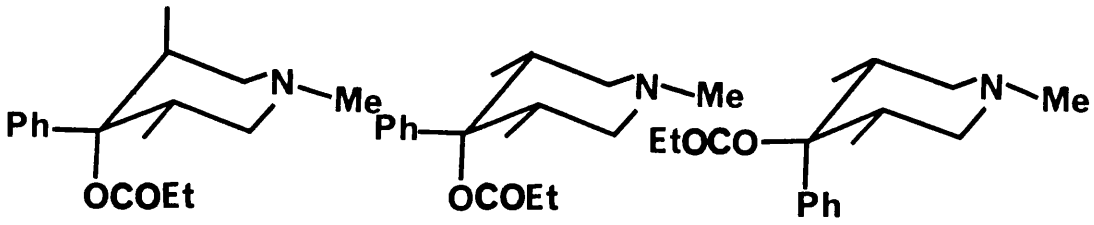
Studying the effect of 3,5-dimethyl substitution on the reversed esters of pethidine, Sorokin[89] reported that three possible diastereoisomers of 50 could exist.

Stereochemical consideration of the three possible diastereoisomers lead to the deduction that one isomer is chiral (50a), and the



(50)

other two meso (5Qb and 5Qc). The chiral isomer (designated γ-) has been shown to be twice as active as morphine in mice, whilst the two meso forms (with a cis - 3,5-dimethyl) were shown to be inactive.



(5Qa) (5Qb) (5Qc)

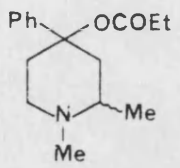
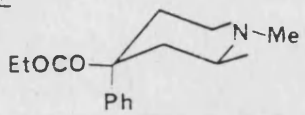
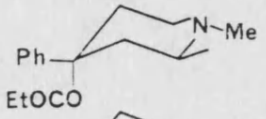
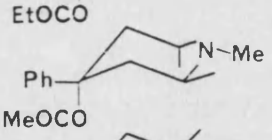
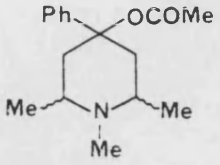
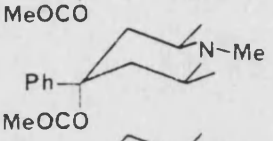
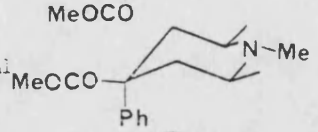
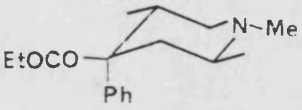
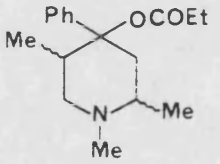
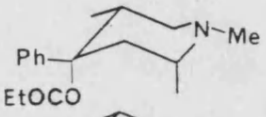
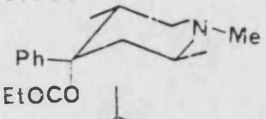
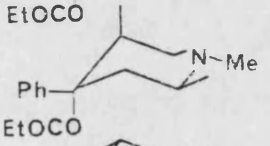
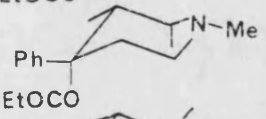
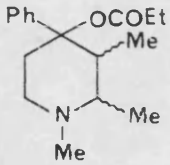
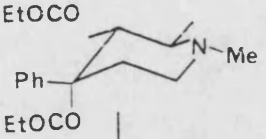
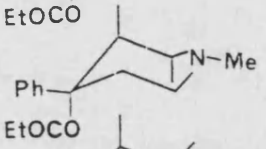
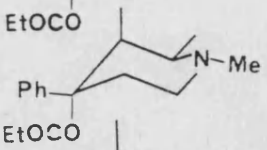
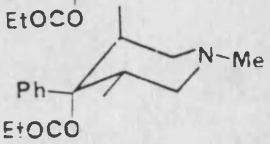
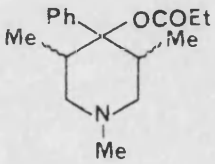
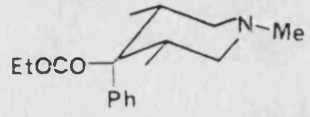
The stereochemistry of the active diastereoisomer (γ-) has been confirmed by Portoghese et al.[90], where an equatorial 4-phenyl chair conformation applies, with a c-3-Me, t-5-Me, r-4-OCOEt configuration.

A summary of the stereochemical data relevant to the 2-methyl and the 2,6-, 2,5-, 2,3- and 3,5- dimethyl analogues of the reversed esters of pethidine is given in Table 2.

C. Absolute configuration and analgesic potency of C-methyl analogues of Reversed Esters of Pethidine reported to date

To complete the analysis of the structure-activity relationship of the reversed esters of pethidine, and so enable a picture to be built up of the stereochemical features of the 4-phenylpiperidines that favour opiate receptor interactions, studies on the two

Table 2 Summary of stereochemical data relevant to the 2-methyl and the 2,6-, 2,5-, 2,3- and 3,5- dimethyl analogues of Reversed Esters of Pethidine

Substituent	Structure	Isomer Designation	Configuration[a]	Analgesic Potency
2-methyl		α-		1.32[b]
		β-		1.37[b]
2,6-dimethyl		Chiral		2.0[b]
		Achiral		Inactive
		Achiral		Inactive
2,5-dimethyl		α-		8[c]
		β-		4[c]
		γ-		2[c]
		δ-		4-6[c]
2,3-dimethyl		α-		1[c]
		β-		Inactive
		γ-		30[c]
		δ-		Inactive
3,5-dimethyl		γ-		2[c]
		meso		Inactive
		meso		Inactive

a. Depicted as the preferred chair conformation; only one enantiomorphic form is shown for chiral molecules.

b. ED_{50} in mg/Kg (parent desmethyl ester = 0.85 mg/Kg)

c. Activity relative to morphine = 1

optical forms of each C-methyl diastereoisomer have been undertaken. Investigations of the two optical forms of alpha- and beta- prodine (see page 26) revealed that when the 3-methyl substituent was equatorial in orientation, as in alpha-prodine (39), substitution on the Pro-4R side (39b) was detrimental to potency, whilst an equatorial 3-methyl substituent on the Pro-4S side (39a) had little influence on analgesic potency (the ED_{50} of 39a is of the same order of magnitude as the parent desmethyl ester). In the case of beta-prodine, (40), with an axially orientated 3-methyl substituent, the potency of the enantiomer in which the substituent was placed on the Pro-4S side (40a) was enhanced, hence indicating an active role of this axial 3-methyl. Table 3 summarises this work.

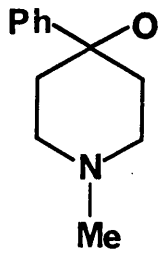
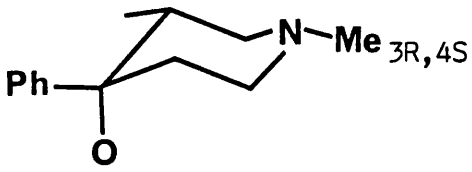
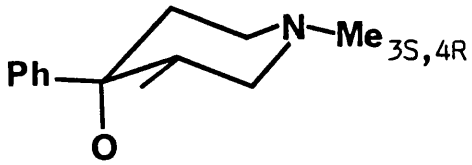
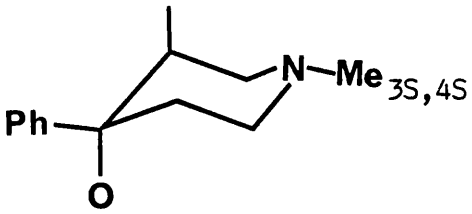
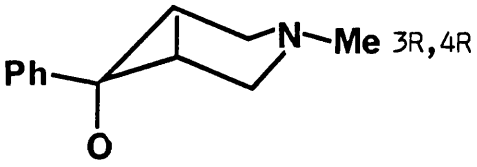
To investigate the effect of the absolute orientation of methyl substitution on analgesic potency, analogues with equatorial methyl substituents only, axial methyl substituents only, and those with mixed axial and equatorial methyl substituents will be considered separately.

{Within this section, acyloxy functions (OCOEt) in the formulae are denoted by O}

a) Equatorial Methyl Substituents

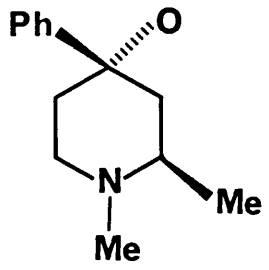
Analogues of the reversed esters of pethidine with equatorial methyl substituents include the β-2-methyl, γ-2,5-dimethyl and the β-2,3-dimethyl derivatives.

Table 3 Analgesic Activity of the podal forms of α- and β-prodine[69]

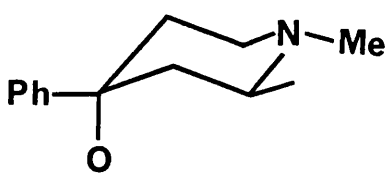
	Structure	Absolute Configuration	ED_{50} (mg/Kg)
Parent desmethyl ester			0.85
alpha-prodine		3R,4S	0.91
alpha-prodine		3S,4R	22.4
beta-prodine		3S,4S	0.25
beta-prodine		3R,4R	3.3

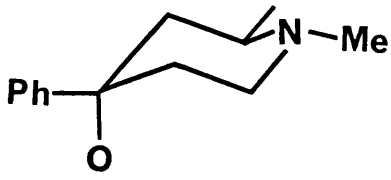
i. The β-2-methyl derivatives

The β-2-methyl derivative (51) of the reversed ester of pethidine is known to exist in a preferred equatorial 4-phenyl chair conformation and the position 2-methyl has an equatorial orientation. Analgesic testing of the racemic ester 51 (partial formula) showed that its potency was slightly less than the parent desmethyl compound. However, separation of the two enantiomers and subsequent analgesic testing revealed that the laevo isomer (51a; with a 2S,4R absolute configuration) had a potency equivalent to the parent ester, while the dextro isomer (51b; with a 2R,4S absolute configuration) was less potent[91].



(51)



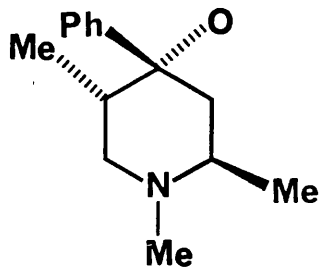


	2S,4R	2R,4S
	(51a)	(51b)
ED_{50} mg/Kg	0.53	5.5

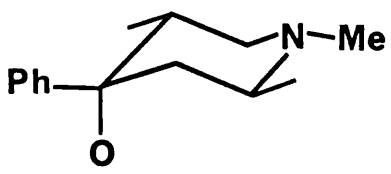
Hence, substitution of a methyl adjacent to the nitrogen on the Pro-4R side of the piperidine molecule has a passive role to play in drug receptor interaction. The fact that the 2R,4S enantiomer was less active than the parent ester indicates that Pro-4S side substitution at position 2 hinders drug interaction with the receptor.

ii. The γ-2,5-dimethyl derivatives

In the γ-2,5-dimethyl analogue of the reversed ester of pethidine (52), both methyl groups have an equatorial orientation. Following the principles established by examination of the 2- and 3-monomethyl derivatives with equatorial substituents, similar consideration of the two enantiomers of (52) revealed the superiority in potency of one antipode over the other[92]. The dextro isomer (52a; 2S,4S,5R) was found to be the more potent antipode as both methyl groups are favourably placed. The laevo isomer (52b; 2R,4R,5S) with both methyl groups in unfavourable orientations was shown to be considerably less active than the parent ester.

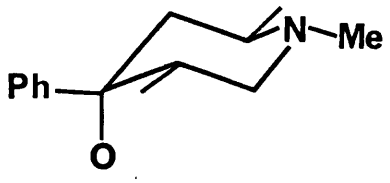


(52)



2S,4S,5R

(52a)



2R,4R,5S

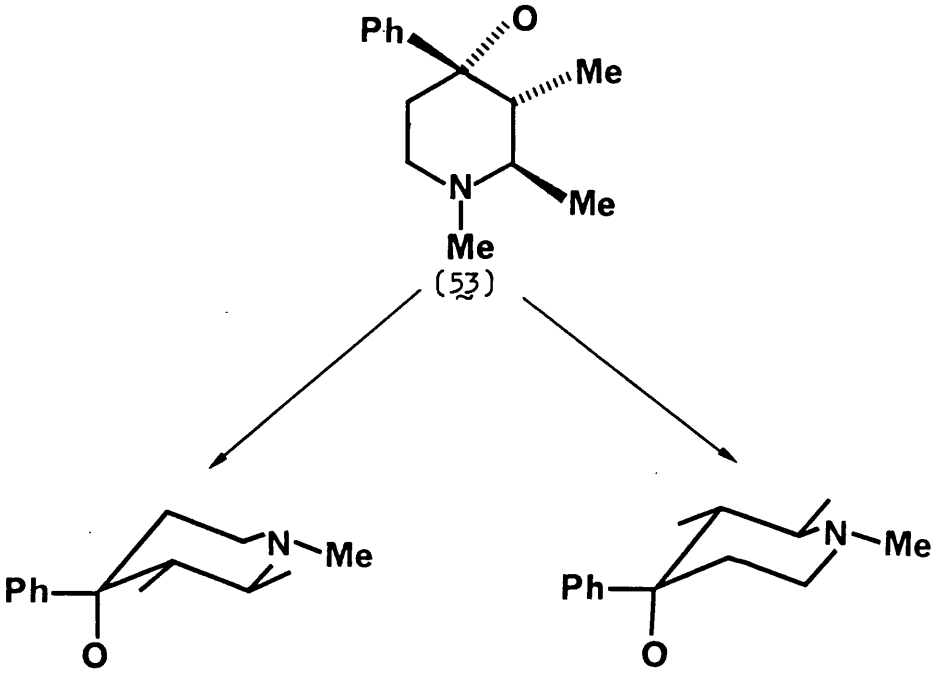
(52b)

ED_{50} mg/Kg	0.94	8.8

The fact that the dextro isomer had a potency equivalent to the parent desmethyl compound is further evidence of a passive role of equatorial methyl substituents.

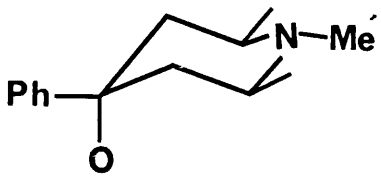
iii. The β-2,3-dimethyl derivatives

The β-2,3-dimethyl derivative (53) has two equatorial methyl groups on the same side of the piperidine molecule. It is therefore impossible to place both methyls in favourable absolute orientations. Hence, if the 2-methyl is in a favourable position (on the Pro-4R side) then the 3-methyl is also on the Pro-4R side and is unfavourable. Similarly, substitution on the Pro-4S side contains one favourable and one unfavoured element (see 53a). This observation explains why the potency of the racemic β-2,3-dimethyl analogue is low (ED_{50}=30.7 mg/Kg, mice HP)[87].

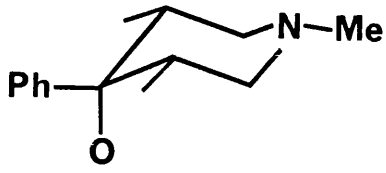


(53) (53a)

In conclusion, equatorial methyl substituents generally have a passive role to play in opiate receptor interactions. This can be justified by the fact that the more active antipodal forms of each diastereoisomeric set have potencies close to that of the parent ester. The arguments given above are further substantiated by analysis of the stereochemical properties of the inactive cis-2,6-dimethyl (54)[77] and cis-3,5-dimethyl (55)[89] analogues. In these two derivatives, methyl substituents of unfavoured absolute orientations are present.



(54)



(55)

Table 4 summarises the data on equatorial methyl substituents.

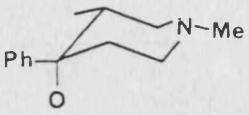
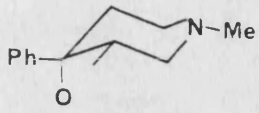
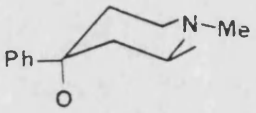
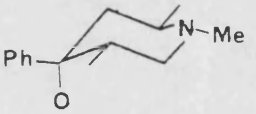
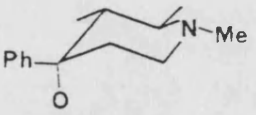
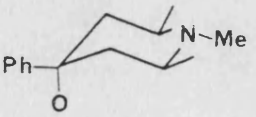
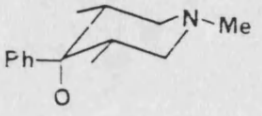
b) Axial Methyl Substituents

Derivatives of the reversed ester of pethidine that illustrate the role of axial methyl groups in opiate receptor interactions include the α-2,5-dimethyl analogue and the γ-2,3-dimethyl analogue.

i. The α-2,5- dimethyl derivative (α-promedol)

Separation of the two optical forms of α-promedol (56) and subsequent analgesic testing indicated that the dextro isomer (56a) was approximately 20 times more active than the parent ester, and also that the laevo isomer (56b) was inactive[93].

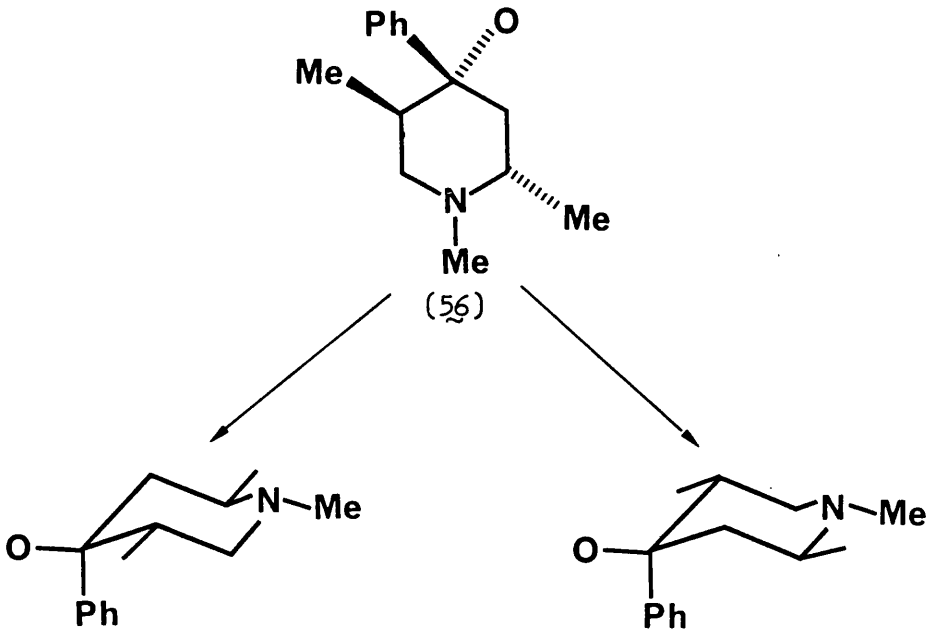
Table 4 A summary of the effect of equatorial C-methyl substitution on analgesic potency in derivatives of Reversed Esters of Pethidine

Substituent	Isomer Designation	Absolute Configuration	Activity ED_{50} (mg/Kg)[a]
3-methyl			
	3R,4S-α-		0.91[b]
	3S,4R-α-		22.4[b]
2-methyl			
	2R,4S-β-		5.5[c]
	2S,4R-β-		0.53[c]
2,5-dimethyl			
	2S,4S,5R-γ-		0.94[b]
	2R,4R,5S-γ-		8.8[b]
2,3-dimethyl			
	Racemic β-	 	30.7[c]
2,6-dimethyl			
	cis		Inactive
3,5-dimethyl			
	cis		Inactive

a. S.C. mice, hot plate test.

b. ED_{50} of parent desmethyl ester = 1.3 mg/Kg

c. ED_{50} of parent desmethyl ester = 0.4 - 0.6 mg/Kg



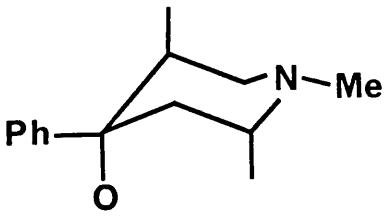
(56)

(+) (-)

(56a) (56b)

ED_{50} (mg/Kg) 0.06 inactive at 50

α-Promedol is considered to exist in an axial 4-phenyl chair conformation with both methyl groups having an equatorial orientation. However, inversion of this axial 4-phenyl chair to the corresponding equatorial 4-phenyl chair gives both methyl groups an axial orientation (57).

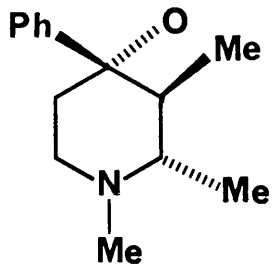


(57)

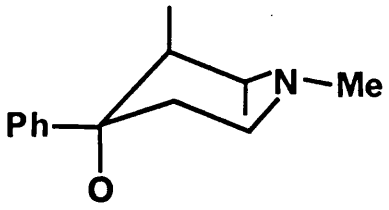
In this conformation, a similarity to β-prodine (40) can be seen. Studies on β-prodine revealed that an axial 3-methyl on the Pro-4S side enhanced activity by a factor of 4 over that of the parent desmethyl ester. This is also the case in (+)-α-promedol, as the axial 3-methyl group is on the Pro-4S side. However, the superiority of potency of (+)-α-promedol over (+)-β-prodine must be due to the influence of an axial 2-methyl group on the Pro-4R side. Therefore, both methyl groups in (+)-α-promedol appear to play an active role in opiate receptor interaction.

ii. The γ-2,3-dimethyl derivative

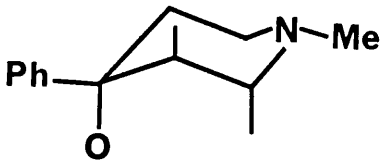
The γ-2,3- dimethyl derivative (58) possesses two axially orientated methyl substituents. The two enantiomers are represented by (58a; Pro-4S side substitution) and (58b; Pro-4R side substitution).



(58)



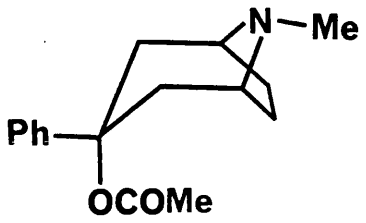
(58a)

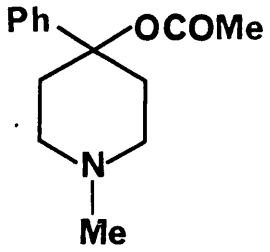


(58b)

Separation of the two antipodal forms has not been undertaken, but it would be expected that the 4S enantiomer (58a) would be more active, as the 3-methyl is in a favourable orientation. In the 4R enantiomer (58b), the axial 3-methyl is of unfavourable orientation (see (-)-β- prodine, page 28)[94].

The 2-methyl substituent, with an axial orientation, also plays an active role in receptor interaction. An axial methyl adjacent to the nitrogen on the Pro-4R side is known to enhance activity (see α-promedol; page 45). However, investigations of the tropane analogue (59) of pethidine reversed acetoxy ester revealed that it exhibits enhanced activity over the parent reversed acetoxy ester of pethidine (60)[95].





(59) (60)

ED_{50} mg/Kg	3.4	4.7

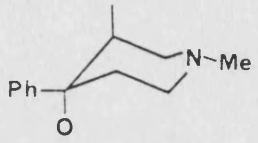
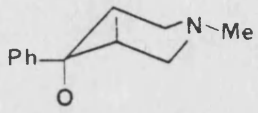
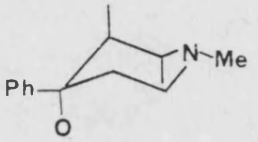
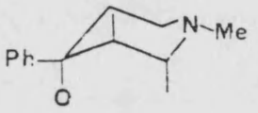
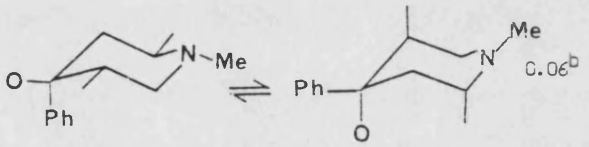
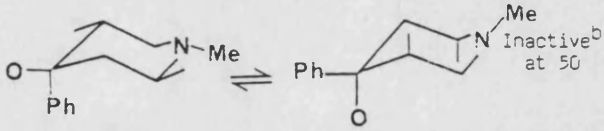
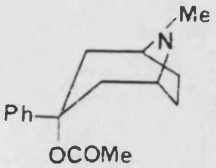
The finding suggests that an axially orientated C-2-methyl on either the Pro-4R or Pro-4S side is not detrimental to analgesic activity.

In conclusion, axially orientated methyl substituents of certain absolute orientation have a profound effect on analgesic activity. An axially placed methyl adjacent to the 4-phenyl on the Pro-4S edge raises potency while a similarly orientated methyl on the Pro-4R edge causes a dramatic decrease in potency. An axially orientated methyl adjacent to nitrogen on either the Pro-4R or Pro-4S edge is also beneficial to potency levels. Table 5 summarises the data on axial methyl substituents.

c) Axial/Equatorial Substituents

With the exception of the γ-3,5-dimethyl analogue of the reversed ester of pethidine, studies on the two optical forms of other C-methyl diastereoisomers with axial and equatorial substituents are lacking. Given below is a consideration of the results

Table 5 A summary of the effect of axial C-methyl substitution on analgesic potency in derivatives of Reversed Esters of Pethidine

Substituent	Isomer Designation	Absolute Configuration	Activity ED_{50} (mg/Kg)[a]
3-methyl	3S,4S-β-		0.25[b]
	3R,4R-β-		3.3[b]
2,3-dimethyl	4S-γ-		c
	4R-γ-		
2,5-dimethyl	(+)-α-		0.06[b]
	(-)-α-		Inactive[b] at 50
Tropane analogue of the reversed acetoxy ester of pethidine			3.4[d]

a. S.C. mice, hot plate test.

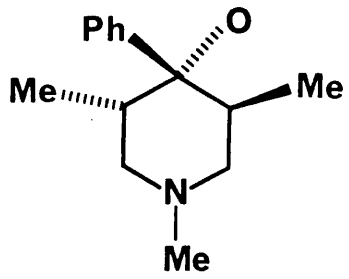
b. ED_{50} of parent desmethyl ester = 1.3 mg/Kg.

c. Racemic mixture, four times as potent as the reversed ester of pethidine

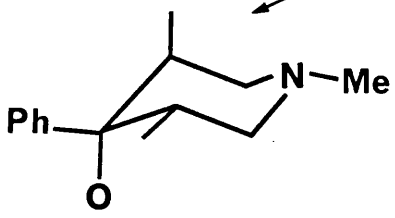
d. ED_{50} of reversed acetoxy ester of pethidine = 4.7 mg/Kg.

obtained from studies on the γ-3,5-dimethyl analogue. A brief assessment of the anticipated results for other C-methyl analogues is given in Table 6.

In the γ-3,5-dimethyl analogue of the reversed ester of pethidine (61), one methyl group has an axial and the other an equatorial orientation. Separation and subsequent analgesic testing of the two enantiomers of 61 revealed the superiority of potency of the dextro isomer (3S,5S; 61a) over the laevo isomer (3R,5R; 61b)[90].

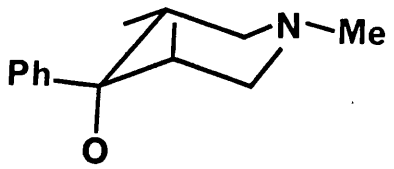


(61)



(+)-3S,5S

(61a)



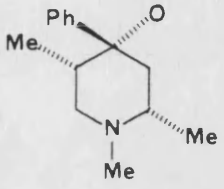
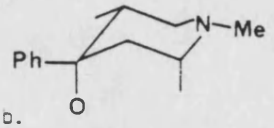
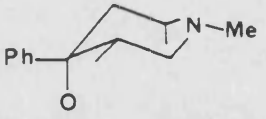
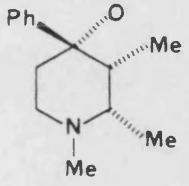
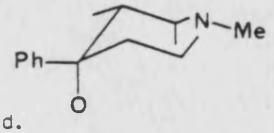
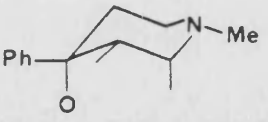
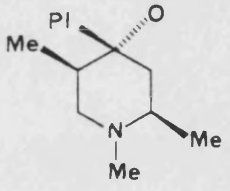
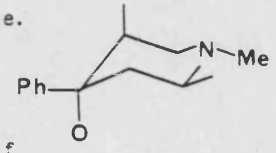
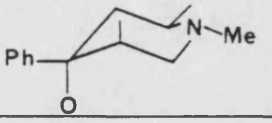
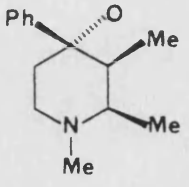
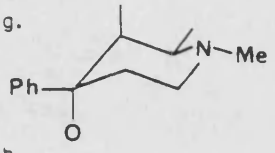
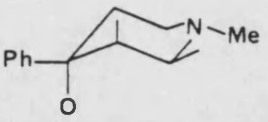
(-)-3R,5R

(61b)

ED_{50} mg/Kg	4.91	25.01

(pethidine 28.8)

Table 6 A SUMMARY OF THE ANTICIPATED EFFECT OF MIXED AXIAL AND EQUATORIAL C-METHYL SUBSTITUTION ON ANALGESIC POTENCY IN DERIVATIVES OF REVERSED ESTERS OF PETHIDINE[94]

Substituent	Structure	Absolute Configuration	Analgesic Activity for Racemic Mixture (ED_{50} mg/Kg)[a]	Notes
β-2,5-dimethyl		a.  b. 	0.6[b]	One equatorial 5- and one axial 2- methyl substituent. Active form expected to be (a), with equatorial 5- methyl within the rear edge.
α-2.3-dimethyl		c.  d. 	1.6[c]	One equatorial 3- and one axial 2- methyl substituent. Active form expected to be (c) with equatorial 3- methyl within the rear edge.
δ-2,5-dimethyl		e.  f. 	Reported as twice active as its corresponding γ-isomer.	One equatorial 2- and one axial 5- methyl substituent. Active form anticipated as (e) with both methyl substitutions in favourable orientations.
δ-2,3-dimethyl		g.  h. 	Inactive	Inactive, as expected due to both methyl groups in unfavourable positions.

a. S.C. mice, hot plate test.

b. ED_{50} of parent desmethyl ester = 0.85 mg/Kg.

c. ED_{50} of parent desmethyl ester = 0.4 - 0.6 mg/Kg.

The dextro isomer possesses a favourably placed axial 3-methyl group (on the Pro-4S side) and an equatorial 5-methyl group which is unfavourable for drug receptor interactions. These observations explain why this antipode is less active than the desmethyl parent ester. In the case of the laevo isomer, neither the equatorial 3-methyl or the axial 5-methyl enhance potency levels and hence explains the low level of activity associated with this podal form.

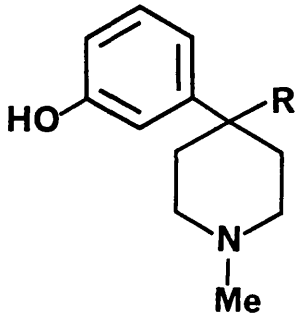
1.5 Concluding Remarks

The features that ensure high levels of potency in the 4-phenylpiperidine class of analgesics have been discussed both from the chemical and stereochemical point of view. However, some ambiguity arises in interpreting the effect on analgesic activity of meta hydroxyl substitution in the aromatic moiety (see section 2.1). The work described in this thesis was undertaken to investigate further examples of phenolic analogues of 4-phenylpiperidine type and tropane type analgesics, the tropanes representing restricted piperidines as a consequence of the fused pyrrolidine ring.

2. DISCUSSION

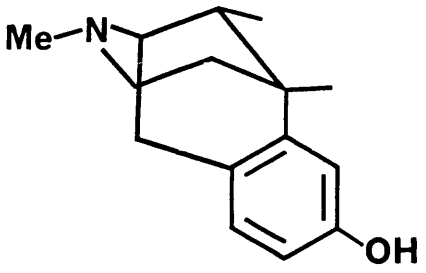
2.1 Aims and Objectives of the Present Work

During the 1950s it was noted that a meta-placed phenolic group as in bemidone (62; R=CO_2Et) and ketobemidone[58] (62; R=COEt) enhanced analgesic activity over their corresponding non-phenolic analogues.

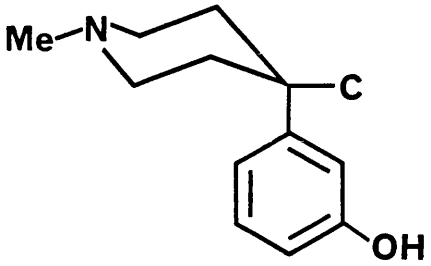


(62)

This observation encouraged the suggestion that the axial-4-phenyl conformation of the piperidines is the active one since it mimics the 4-aryl piperidine moiety of the morphine skeleton (see 63)[96].



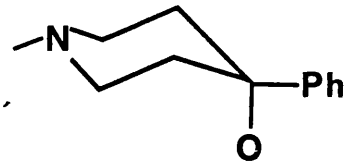
Morphine - Partial Formula



4-Arylpiperidine - Partial Formula

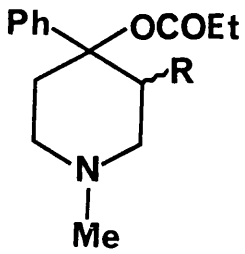
(63)

However, studies on the reversed esters of pethidine with one or two C-methyl substituents placed at various positions around the alicyclic ring, has yielded data consistent with the equatorial-4-phenyl chair as the preferred conformation (64; see section 1.4.2.4). Furthermore, as outlined in section 1.4.2.2, the introduction of a meta-placed hydroxy into the phenyl substituent of the reversed ester of pethidine (65; R=H), α-prodine (65; R=Me, with c-3-Me, r-4-OCOEt), β-prodine (65, R=Me, with t-3-Me, r-4-OCOEt), and the two allylprodines (65; $R=CH_2-CH=CH_2$), all potent analgesics, leads to a virtual loss of activity, either as agonists or antagonists[56,57].



Pethidine Reversed Esters - Partial Formula

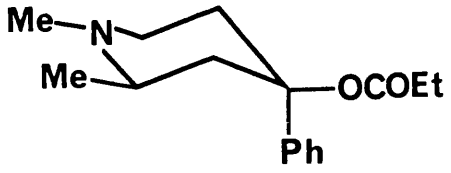
(64)



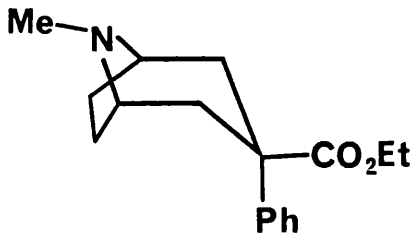
(65)

It would seem, therefore, that analgesics based on 4-aryl-piperidine with C_4-carbon substituents associate with opiate receptors in the axial-4-aryl chair conformation, which is a mode closely analogous to that of morphine. It is consistent that introduction of a meta-OH function into such C_4-carbon piperidines should enhance analgesic potency. The pethidine reversed esters, on the other hand, which possess C_4-oxygen functions, seem to associate with opiate receptors in a different manner, involving an equatorial 4-phenyl chair conformation which will not tolerate a phenolic substituent.

The aim of this work is to secure compounds of specific configuration that will challenge these proposals. The compounds required are those which are phenolic analogues of both C_4-carbon and C_4-oxygen 4-phenylpiperidines, with features ensuring high preference for axial-4-aryl conformers. Included in this group of compounds are the phenolic analogues of α-2-methyl pethidine reversed ester (66)[75] and the phenolic analogue of tropane (67) which has an aromatic substituent positioned α-(and axial)[97].



(66)



(67)

One other aim of the present thesis is to obtain further data on the optical enantiomers of the reversed ester of pethidine. To this end, resolution of α-1,2-dimethyl-4-phenylpiperidin-4-ol was undertaken.

The work in this thesis therefore entailed:

1. The synthesis of required compounds;

2. Separation of isomers;

3. Configurational and conformational assignments using spectroscopic techniques; and

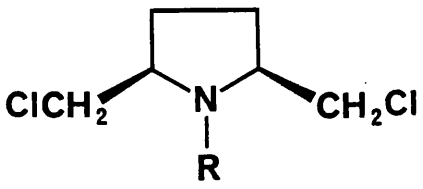
4. Pharmacological evaluation.

2.2 The Tropanes

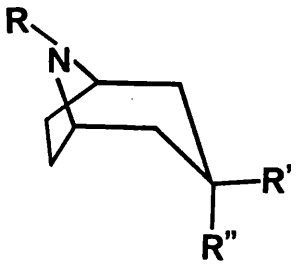
2.2.1 Attempted synthesis of ethyl 3α-(3-hydroxyphenyl)-3β-tropane carboxylate and ethyl 3β-(3-hydroxyphenyl)-3α-tropane carboxylate.

2.2.1.1 Introduction

In 1961, Cignarella et al.[98] reported that cis-N-tosyl-2,5-bis(chloromethyl)pyrrolidine (68; R=tosyl) and phenylacetonitrile in the presence of $NaNH_2$ afforded a single compound (69; R=tosyl, R'=CN, R''=Ph) in 28% yield. This in turn was converted to the β-ester (69; R=Me, R'=CO_2Et, R''=Ph). Further studies in 1974 by Daum et al.[99] reported that cis-N-benzyl-2,5-bis(chloromethyl)-pyrrolidine (68; R=CH_2Ph) and phenylacetonitrile in the presence of NaH in D.M.F. yielded a 3:1 mixture of the compounds (69; R=CH_2Ph, R'=CN, R''=Ph) and (69; R=CH_2Ph, R'=Ph, R''=CN). They succeeded in separating this epimeric mixture and converted each epimer to the corresponding tropane analogue (69; R=Me, R'=CO_2Et, R''=Ph) and (69; R=Me, R'=Ph, R''=CO_2Et) of pethidine.



(68)



(69)

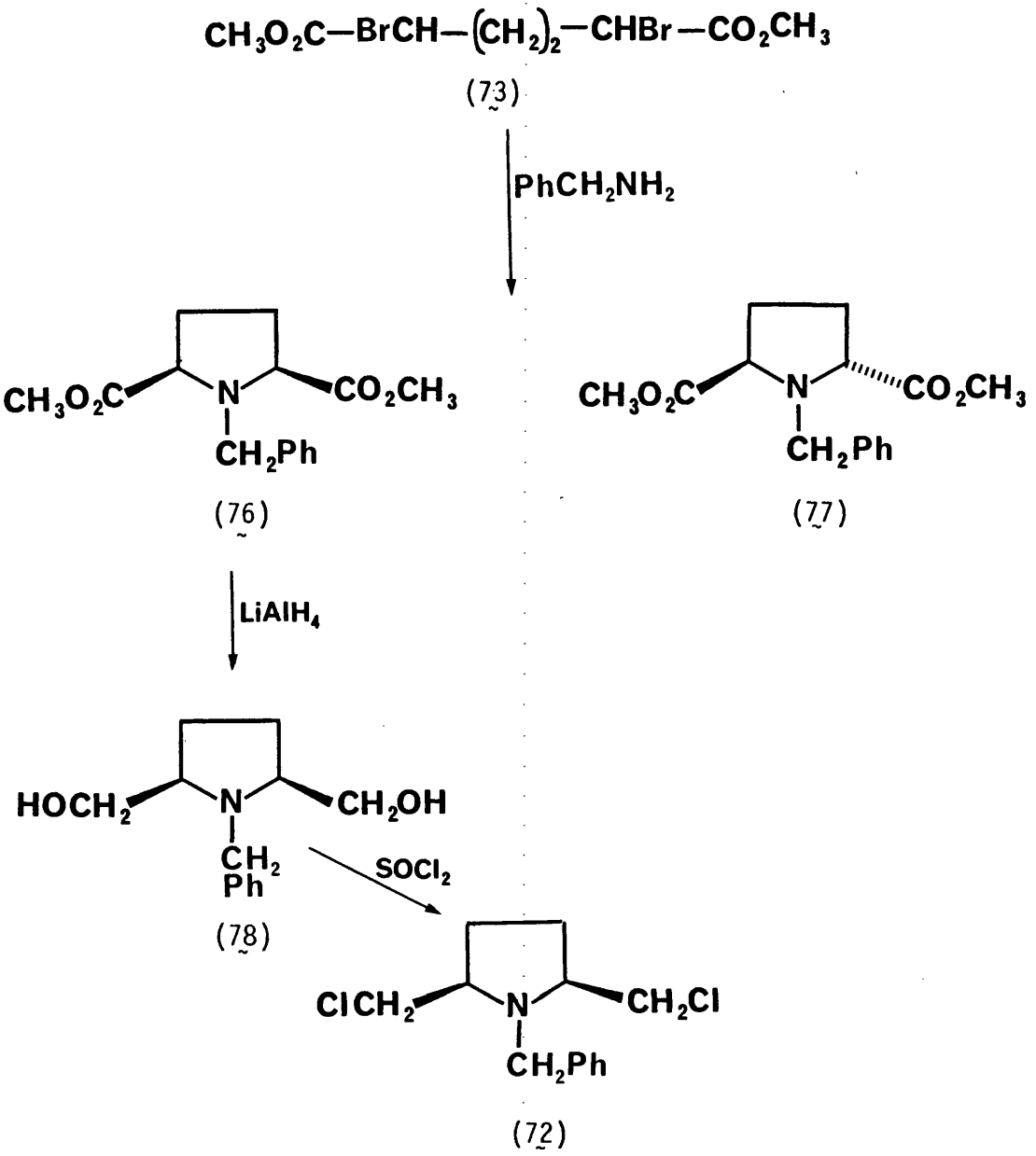
As part of this present work, modification of the method described by Daum et al.[99] utilizing m-methoxyphenylacetonitrile and cis-N-benzyl-2,5-bis(chloromethyl)pyrrolidine was employed.

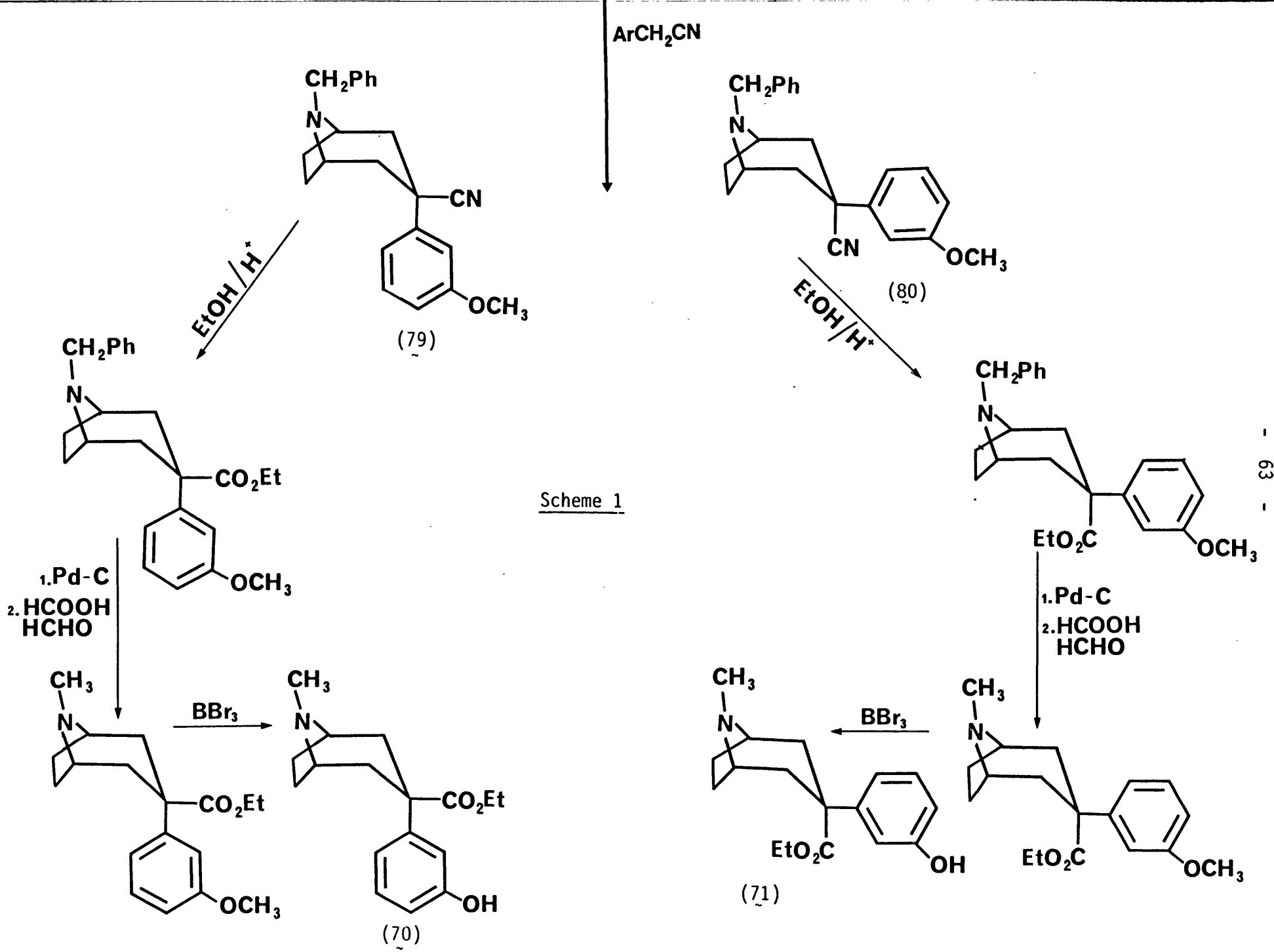
2.2.1.2 Synthesis and Chemistry

The proposed route of synthesis for the two phenolic tropane analogues (70) and (71) of pethidine is outlined in Scheme 1.

A. The synthesis of cis-N-benzyl-2,5-bis(chloromethyl)-pyrrolidine

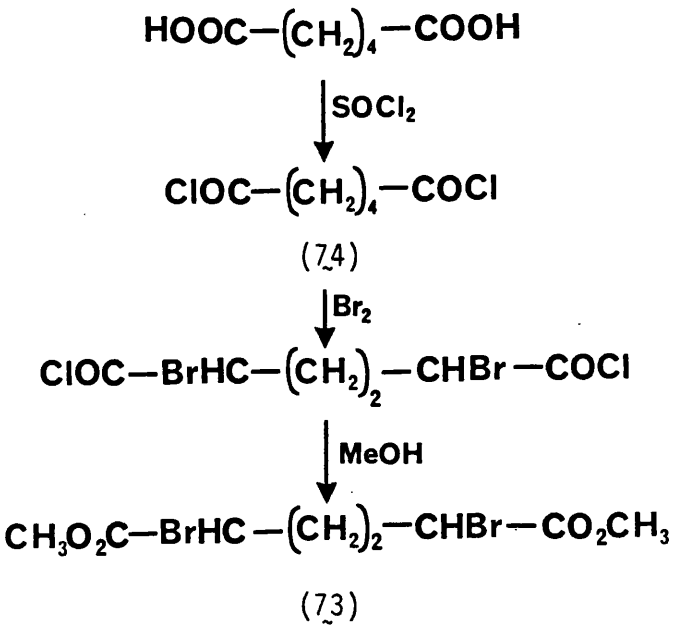
The first step leading to the intermediate cis-N-benzyl-2,5-bis(chloromethyl)pyrrolidine (72; Scheme 1) in the synthesis of the target compounds (70 and 71) involved the condensation of methyl meso-αα'-dibromoadipate (73) and benzylamine.


CH3O2C—BrCH—(CH2)2—CHBr—CO2CH3
(73)
PhCH2NH2
CH3O2C
N
CO2CH3
CH2Ph
(76)
CH3O2C
N
CO2CH3
CH2Ph
(77)
LiAlH4
HOCH2
N
CH2OH
CH2
Ph
(78)
SOCl2
ClCH2
N
CH2Cl
CH2Ph
(72)


ArCH2CN
CH2Ph
N
CN
OCH3
(79)
(80)
EtOH/H+
CO2Et
1.Pd-C
2.HCOOH
HCHO
CH3
BBr3
OH
EtO2C
(70)
(71)

Scheme 1

Methyl meso-αα'-dibromoadipate was prepared by the procedure described by Blackman and Baltzly[100]. This involved the bromination of adipoyl chloride (74; prepared by the action of thionyl chloride on adipic acid) followed by reaction with methanol (Scheme 2). The bromination of adipoyl chloride proved practically

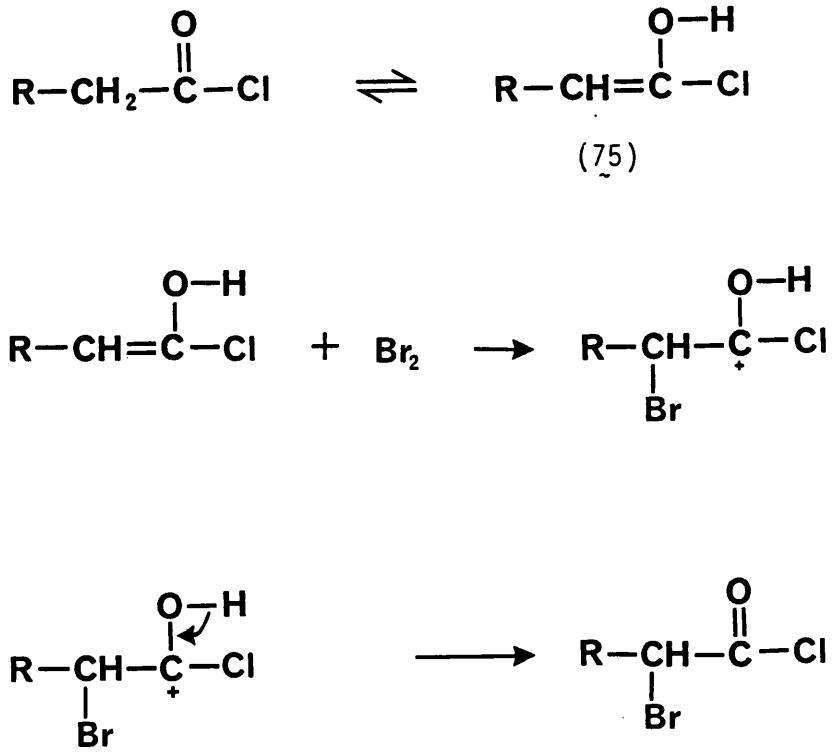


Scheme 2

difficult, often resulting in charring of the product. To overcome this problem it was necessary to perform the reaction on small aliquots of adipoyl chloride with careful control of the temperature of the reaction medium.

This bromination, a type of Hell-Volhard-Zelinsky reaction[101-103], is positionally selective and results in α-bromination only. Although explanations of the mechanism of the

Hell-Volhard-Zelinsky reaction have been numerous[104,105], the mechanism is usually regarded as proceeding through the enol (75), as outlined in Scheme 3[106].



(75)

Scheme 3

Cyclization of methyl meso-αα'-dibromoadipate with benzylamine led to an isomeric mixture of cis- and trans-N-benzyl-2,5-dicarbomethoxypyrrolidine (76 and 77; Scheme 1), in the approximate ratio 2:1 (as judged by ^{1}H-n.m.r. O-CH_3 signal intensity and substantiated by ^{13}C-n.m.r. relative signal intensities). Separation of these two isomers was achieved by fractional crystallisation of their hydrochloride salts.

The stereochemistry of the two products was established from their ^{1}H-n.m.r. spectral characteristics (at 400MHz), notably the multiplicity of the $\underline{N}$-C$\underline{H}_2$ signal. The ^{1}H-n.m.r. spectrum of the major isomer (Table 10, No.1) exhibited a sharp singlet at δ3.90 for the $\underline{N}$-C$\underline{H}_2$ signal, indicative of two magnetically equivalent protons. However, the spectrum of the minor isomer (Table 10, No.2) showed a two proton AB quartet pattern centred at δ3.95 for one proton and 3.78 for the other (J=13Hz), a feature associated with two non-equivalent, mutually coupled protons (see Fig.2).

An AB quartet pattern arises when two non-equivalent protons couple with each other, that is, the protons exhibit a geminal coupling of the order 12-18Hz, while the chemical shift difference between them is small. As an example to illustrate the nature of an AB quartet, the hypothetical case of two non-equivalent methylene protons H_A and H_B will be considered. The non-equivalence of these two protons can be caused by one of three situations:

1. the methylene group is part of a ring system,
2. the methylene group is adjacent to an asymmetric centre,
3. the methylene group is part of an aliphatic chain in which there is restricted rotation.

The two protons H_A and H_B have a chemical shift difference of $\Delta\delta AB$ and a geminal coupling constant J_{AB}, where $J_{AB} >> \Delta\delta AB$. This situation gives rise to a pattern of four perturbed lines representing these two protons, as illustrated in Fig.3.

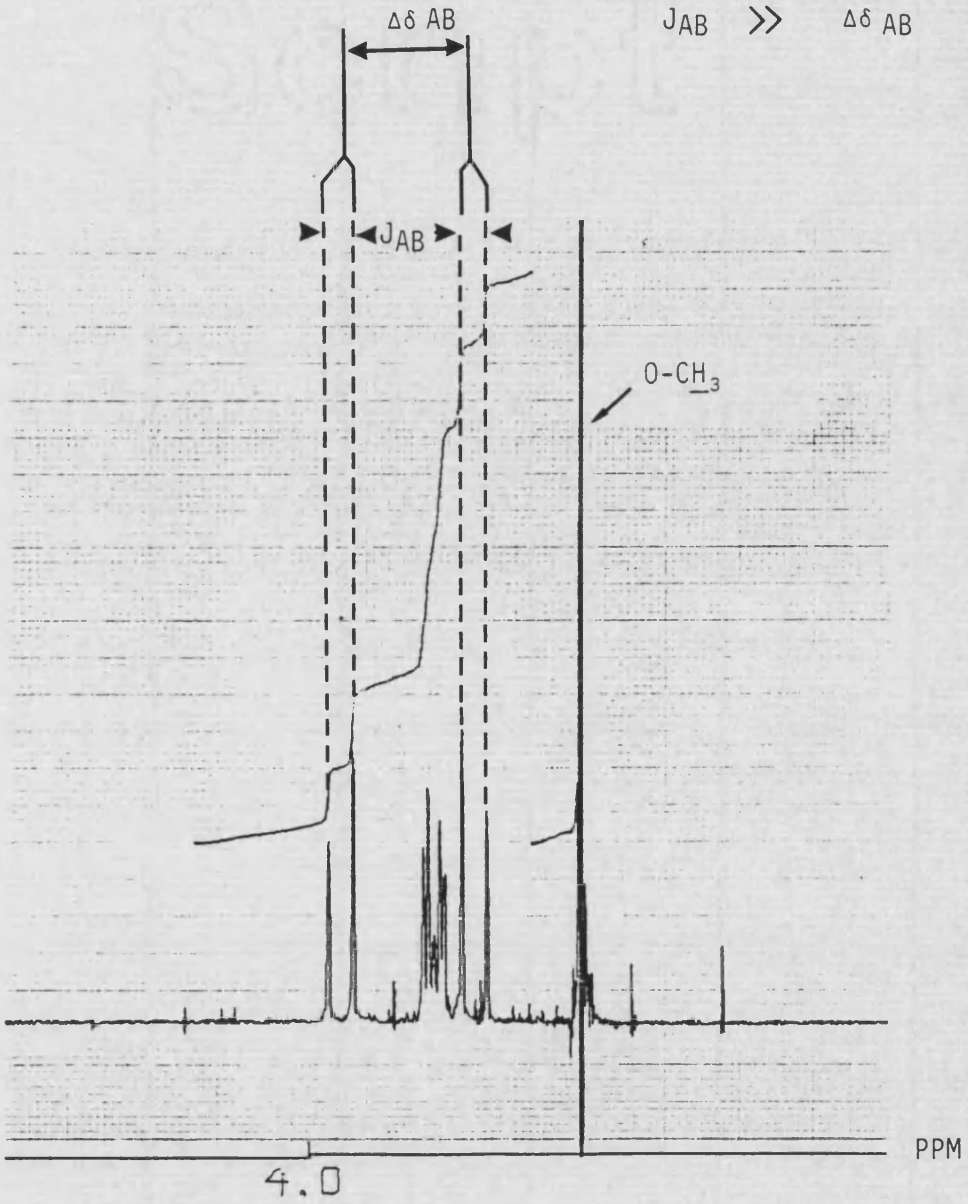


Figure 2 Partial ^{1}H-n.m.r. spectrum (at 400 MHz) to illustrate AB quartet pattern of non-equivalent methylene protons in trans-N-benzyl-2,5-dicarbomethoxypyrrolidine.

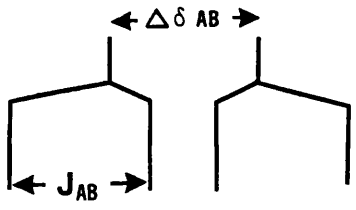
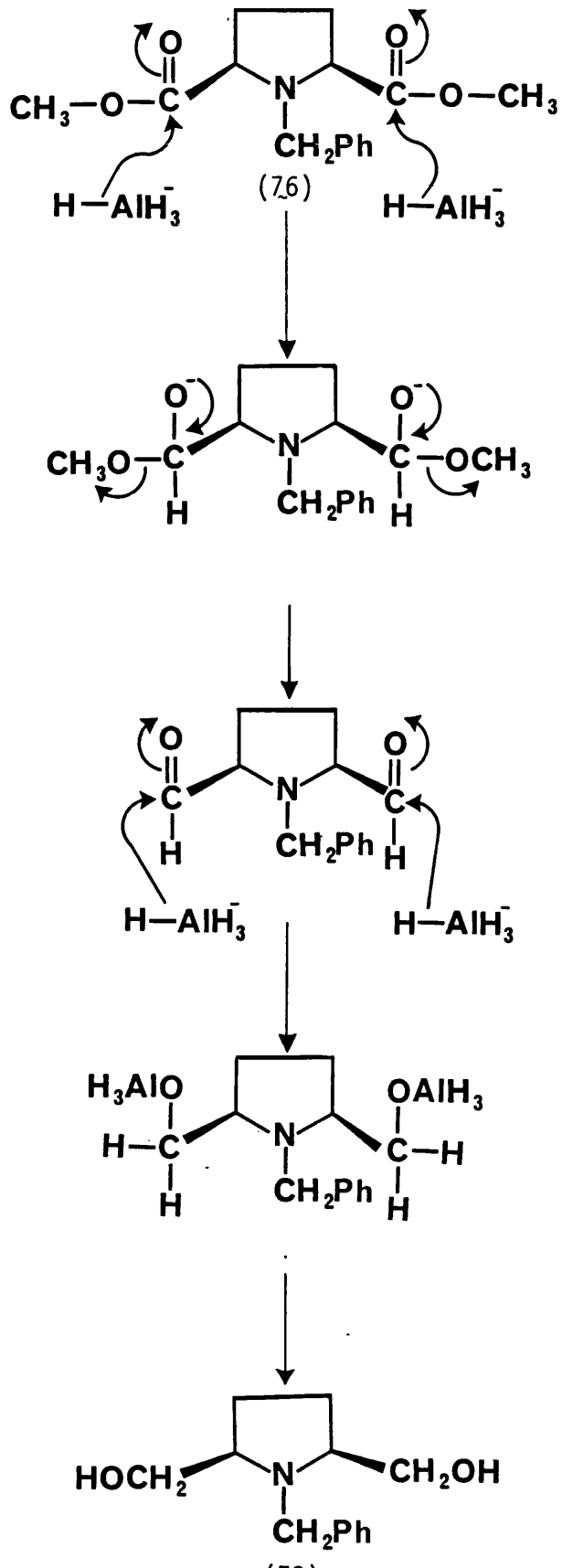


Figure 3

Examination of Dreiding models of the two isomeric forms of N-benzyl-2,5-dicarbomethoxypyrrolidine (76 and 77) suggests that while the cis isomer possesses two equivalent protons, in the trans form the two protons are not equivalent due to restricted rotation about the N-CH_2 bond. Therefore, the ^{1}H-n.m.r. data of the major isomer is consistent with a cis stereochemistry and that of the minor isomer consistent with a trans stereochemistry. In accord with this finding, the ^{1}H-n.m.r. spectrum of the minor isomer (trans form) showed far greater signal complexity, as expected for this non-symmetrical molecule.

The ^{13}C-n.m.r. and IR spectra for the cis-isomer were consistent with the assigned structure (76).

Having isolated and characterised cis-N-benzyl-2,5-dicarbomethoxy-pyrrolidine, nucleophilic reduction of this ester with $LiAlH_4$ in tetrahydrofuran proceeded smoothly yielding the alcohol (78; Scheme 1)[109]. $LiAlH_4$ is a powerful reducing agent, capable of reducing the C=O group in aldehydes, ketones, acids, esters and amides[107]. The effective reducing agent is AlH_4^- which acts as a powerful hydride ion, H^-, donor. Mechanistically this reduction proceeds as shown in Scheme 4.



(7.6)

(7.8)

Scheme 4

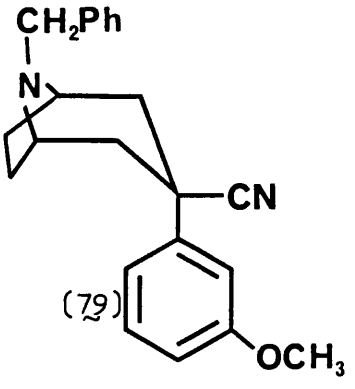
The ^{13}C-n.m.r. and IR spectra of the reduced product indicated absence of the carbonyl group (no signals at δ175.9ppm and 1740 cm^{-1} respectively), and were consistent with the assigned structure.

The ^{1}H-n.m.r. spectrum was consistent with a cis stereochemistry as indicated by a sharp singlet at δ3.86 for the N-CH_2 protons.

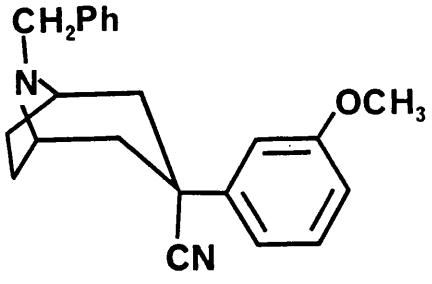
This alcohol on reaction with thionyl chloride in toluene gave cis-N-benzyl-bis(chloromethyl)pyrrolidine (72; Scheme 1) as the hydrochloride salt which separated on addition of ether. Data collated on this compound (^{13}C-n.m.r., ^{1}H-n.m.r. and IR) were consistent with the assigned structure and stereochemistry. In addition, the melting point and solubility characteristics of this cis-isomer correlated well with reports in the patent literature[108,109].

B. Attempted cyclization of cis-N-benzyl-2,5-bis(chloromethyl)pyrrolidine and m-methoxyphenylacetonitrile

As outlined in Scheme 1, cyclization of cis-N-benzyl-2,5-bis(chloromethyl)pyrrolidine (72) with m-methoxyphenylacetonitrile was expected to yield an epimeric mixture of the two tropane derivatives (79) and (80).



(79)



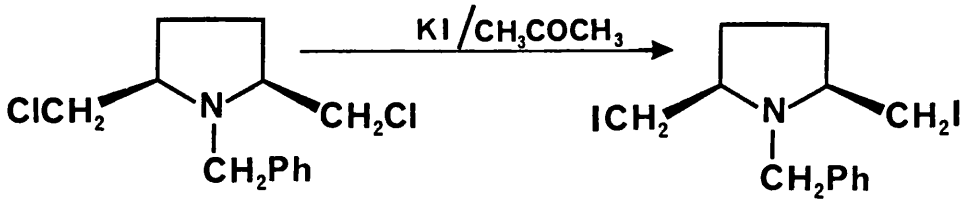
(80)

However, in the course of these studies numerous attempts to effect this cyclization failed to generate the required tropane derivatives.

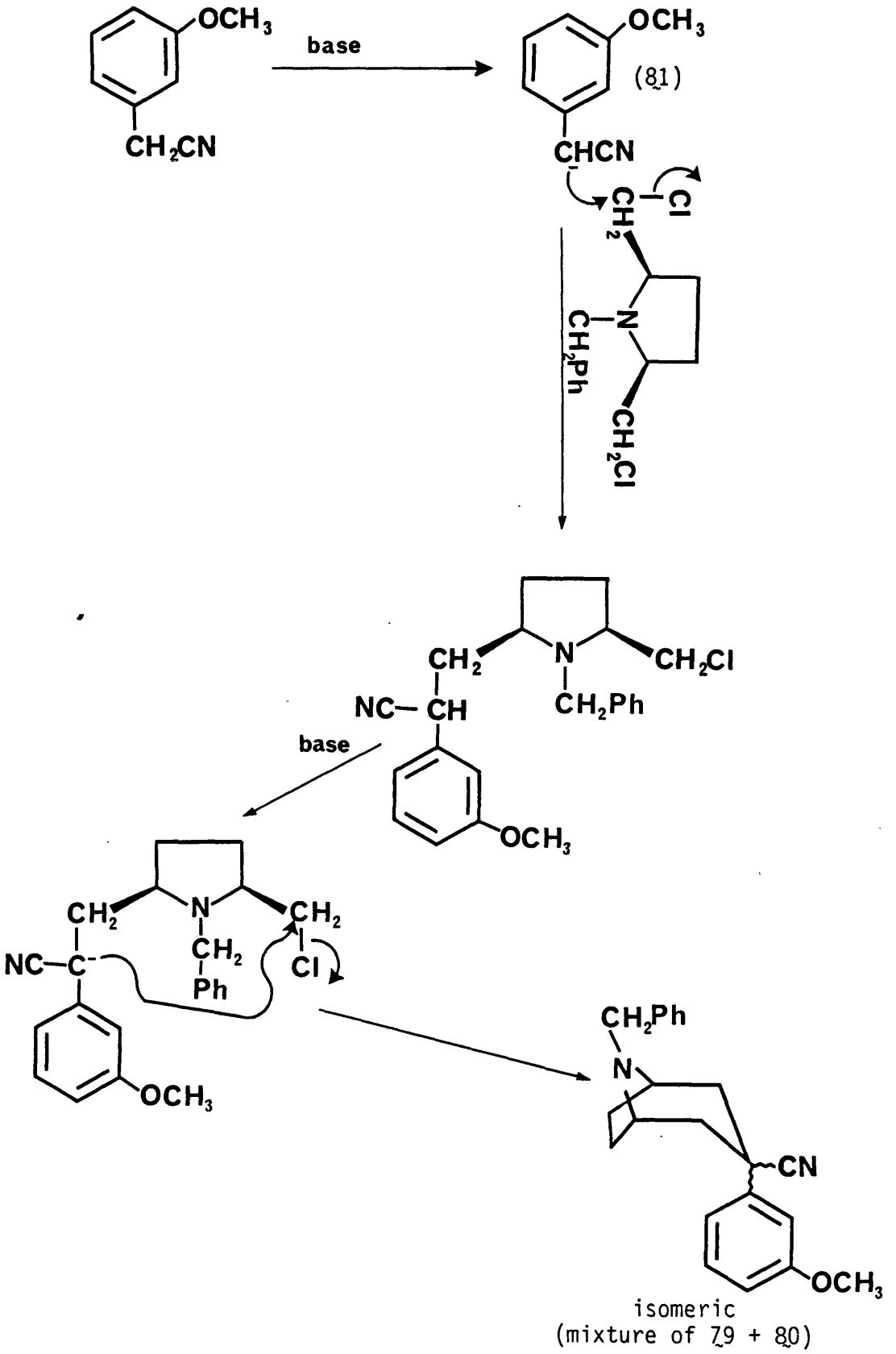
The reaction was expected to proceed as outlined in Scheme 5, involving the formation of the carbanion (81) due to proton extraction by bases such as NaH, $NaNH_2$ or Na metal. Ring cyclization by nucleophilic alkylation would then occur.

Table 7 lists the conditions and bases used in this attempted unsuccessful cyclization. In all cases the reactions yielded dark viscous oils, the t.l.c. and ^{13}C-n.m.r. spectra of which showed the products to be complex mixtures which proved intractible. The possibility that a meta placed methoxy group hindered carbanion formation was investigated by utilizing phenylacetonitrile in the cyclization. In contrast to the reports by Daum et al.,[99] this cyclization (using NaH in D.M.F.) also failed.

Replacement of the chlorine groups in (72) with iodine (via the



(72) (82)


OCH3
base
CH2CN
(81)
CHCN
CH2
Cl
N
CH2Ph
CH2Cl
NC
CH
base
OCH3
CH2
N
CH2Cl
CH2Ph
NC
C
CH2
Ph
Cl
OCH3
CH2Ph
N
CN
OCH3
isomeric
(mixture of 79 + 80)

Scheme 5

Table 7 CONDITIONS AND BASES USED IN THE ATTEMPTED UNSUCCESSFUL CYCLIZATION OF CIS-N-BENZYL-BIS(CHLOROMETHYL)PYRROLIDINE WITH m-METHOXYPHENYLACETONITRILE

Base	Solvent	Molar Proportions			Time [b] (hrs)
		base	(82)	a	
$NaNH_2$	Toluene	0.3	0.1	0.12	2
					4
					12
		0.6	0.1	0.12	12
					24
NaH (60% w/w dispersion in mineral oil)	D.M.F.	0.42	0.09	0.14	2
					10
					24
		0.84	0.09	0.14	48
Lithium Di-isopropylamine	T.H.F.	n-butyl lithium: 0.27 di-isopropylamine: 0.23	0.122	0.32	24

a: m-methoxyphenylacetonitrile

b: at reflux temperature

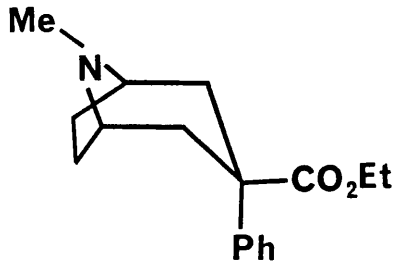
Finklestein reaction)[110] to give cis-N-benzyl-2,5-bis(iodomethyl)-pyrrolidine (82), a compound with a leaving group that can be more readily displaced than chlorine[111], also failed to effect cyclization with phenylacetonitrile.

At this stage in the work the synthetic approach expressed in Scheme 1 was abandoned.

2.2.2 The synthesis of ethyl 3α-(3-hydroxyphenyl)-3β-tropane carboxylate and corresponding N-alkylated nortropanes

2.2.2.1 Introduction

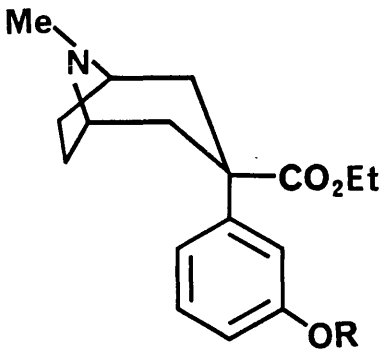
Following the unsuccessful attempt of the synthesis of the epimeric tropane derivatives (70) and (71; Scheme 1), attention was given to the synthetic procedure described by Bell and Archer[97] on the original synthesis of the 3α-phenyl tropane analogue of pethidine (67).



(67)

Modification of this approach utilizing 3-bromoanisole was undertaken, with the aim of producing the single tropane derivative

(83; R=Me). O-Demethylation of this derivative would thus yield the required 3α-phenolic tropane analogue (83; R=H) of pethidine.



(83)

Before considering the synthesis and stereochemistry of this group of compounds, attention will be given to the conformational and configurational analysis of 3,3-disubstituted tropanes.

2.2.2.2 Conformational and configurational analysis of 3,3-disubstituted tropanes

The conformational preference of the tropane derivatives produced in this work was provided by analysis of the ^{1}H-n.m.r. data.

Assignment of the appropriate conformation to each tropane derivative was made by analysis of the width of half the maximum height ($W_{\frac{1}{2}}$) of the 1(5)-H signal[112,113]. Throughout this tropane series the coupling between the 6(7)-methylene protons and the 1(5)-H is considered to be constant. However, the magnitude of the coupling constant (^{3}J) between the 1(5)-H and the 2(4)-H protons in the boat and chair conformation differs considerably.

The magnitude of ^3J in this tropane series largely depends on the dihedral angle (Ø) between the 1(5)-H and the 2(4)-H protons, as described by Karplus[114]. The relationship between the coupling constant (^3J) and the dihedral angle (Ø) is given by:

$$^3J = \begin{cases} 8.5 \cos^2 Ø - 0.28 & 0^0 \leqslant Ø \leqslant 90^0 \\ 9.5 \cos^2 Ø - 0.28 & 90^0 \leqslant Ø \leqslant 180^0 \end{cases}$$

Thus, the coupling constant (^3J) depends upon the carbon-hydrogen bond angle (see Fig.4).

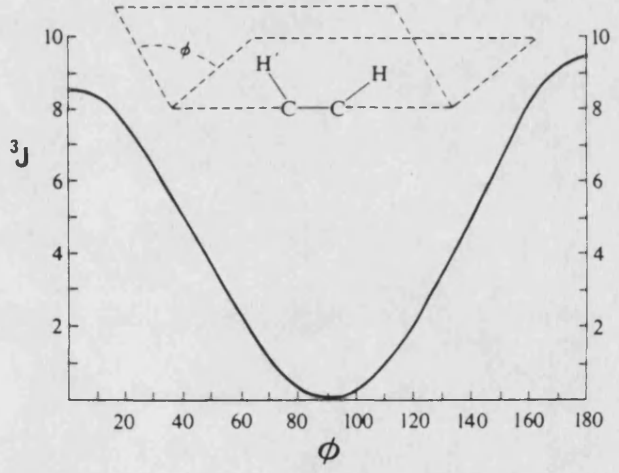
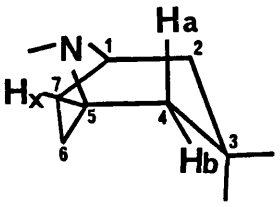
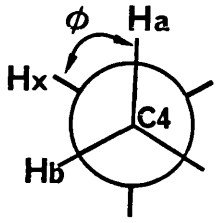


Figure 4: Relationship between the dihedral angle Ø, and vicinal coupling constants

In the chair conformation (84), the couplings are small (Fig.5) and hence the 1(5)-H resonance signal is narrow[115].



NEWMAN PROJECTION
(viewed along 4,5 bond)

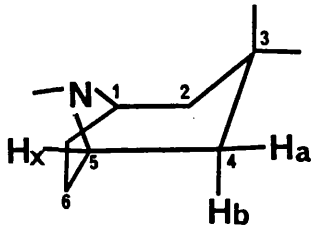


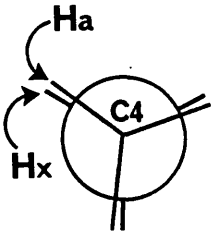
(84)

Figure 5

However, in the boat conformation (85), the 1(5)-H and 2(4)-H protons are eclipsed and so the coupling is large, giving rise to a broad 1(5)-H resonance signal (Fig.6)[116].

NEWMAN PROJECTION
(viewed along 4,5 bond)



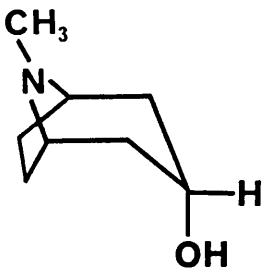


(85)

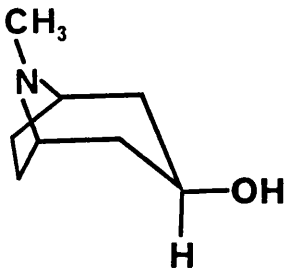
Figure 6

To illustrate the application of these principles, model boat and chair tropanes are presented below.

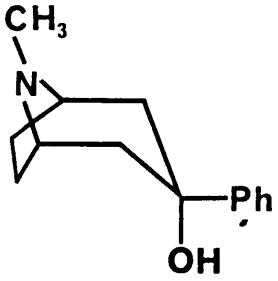
Tropine (86), pseudotropine (87) and 3β-phenyltropan-3α-ol (88) are considered to exist in a preferred chair conformation[117-121]. Examination of the respective ^{1}H-n.m.r. spectra revealed that the $W_{\frac{1}{2}}$ value of the 1(5)-H resonance was in the range 9 - 10Hz, and therefore is taken to be diagnostic of a tropane derivative existing in a chair (or flattened chair) conformation[122].



(86)

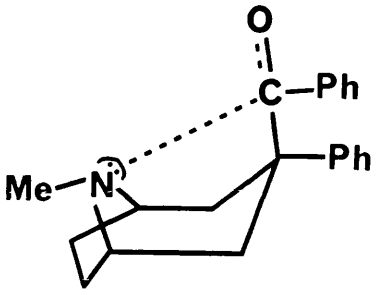


(87)



(88)

3α-Phenyl-3β-tropanylphenylketone (89) is considered to be a tropane derivative that exists in a boat conformation (U.V. and IR evidence)[123]. The ^{1}H-n.m.r. spectrum displayed a 1(5)-H signal with $W_{\frac{1}{2}}$=18Hz[122], a value taken as diagnostic of a boat conformation.



(82)

With the availability of 400MHz ^{1}H-n.m.r., further information to substantiate the assigned conformation was achieved by analysis of the resonance appearance of the axial 2(4)-H signal. Vicinal coupling in the boat is large while in the chair it is small.

^{1}H-n.m.r. and ^{13}C-n.m.r. spectroscopy also provides evidence in relation to the configuration at C-3, that is, the nature of the axially orientated group. This analysis is based on the chemical shift difference (Δ) between the <u>exo</u> and <u>endo</u> 6(7)-methylene protons in the ^{1}H-n.m.r., and the chemical shifts of the C_6C_7 carbon resonance in the ^{13}C-n.m.r.

The following examples illustrate how establishing the configuration was undertaken using ^{1}H-n.m.r. spectroscopy. The application of ^{13}C-n.m.r. in configurational assignments is discussed on pages 93 and 100.

(a) The influence of an axially orientated hydroxy group at C-3 on the 6(7)-methylene protons can be discerned by examination of the ^{1}H-n.m.r. data (notably the resonance position of the 6(7)-hydrogens) for tropine (86) and pseudotropine (87). In tropine (86), with an axial 3-OH, the endo 6(7)-protons are deshielded and hence are separated from the exo 6(7)-protons. In pseudotropine (87), with an equatorial 3-OH, this separation of signals is not seen[116,124].

(b) Similar consideration of the resonance position of the 6(7)-methylene hydrogens in 3-substituted tropanes with an axial C-3 carbonyl group (as in a ketone or an ester) allows its orientation to be confirmed. In the axial orientation it exerts a deshielding influence[125] on the endo 6(7)-protons as a result of magnetic anisotropic effects that are induced[126]. In the equatorial orientation, the carbonyl group would not exert this deshielding influence. Application of this finding, as in α-ecgonine ester (90), is considered on page 88.

(c) Examination of the ^{1}H-n.m.r. data to elucidate the effect of an axially orientated aromatic ring in 3,3-disubstituted tropanes indicates a shielding effect on the endo 6(7)-protons[127]. In this axial orientation, the plane of the aromatic ring is at right angles to a plane passing through nitrogen and C-3 of the piperidine ring[128] and sets up a shielding influence (see Fig.7).

TROPANE
(partial formula)

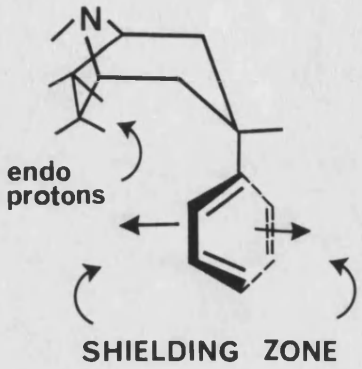


Figure 7

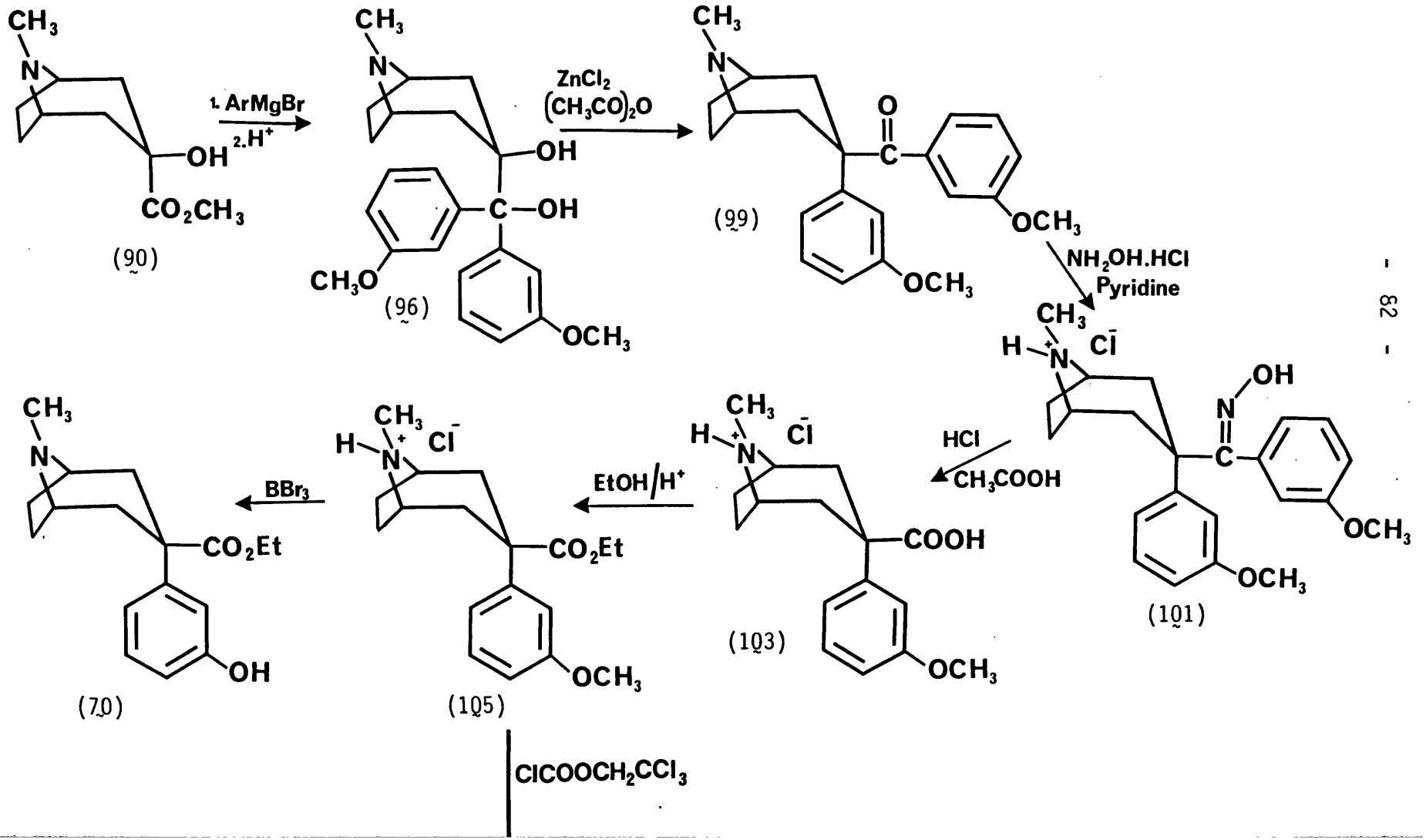
Using these principles, it was possible to elucidate the nature of the axial group at C-3 in the tropane series synthesised.

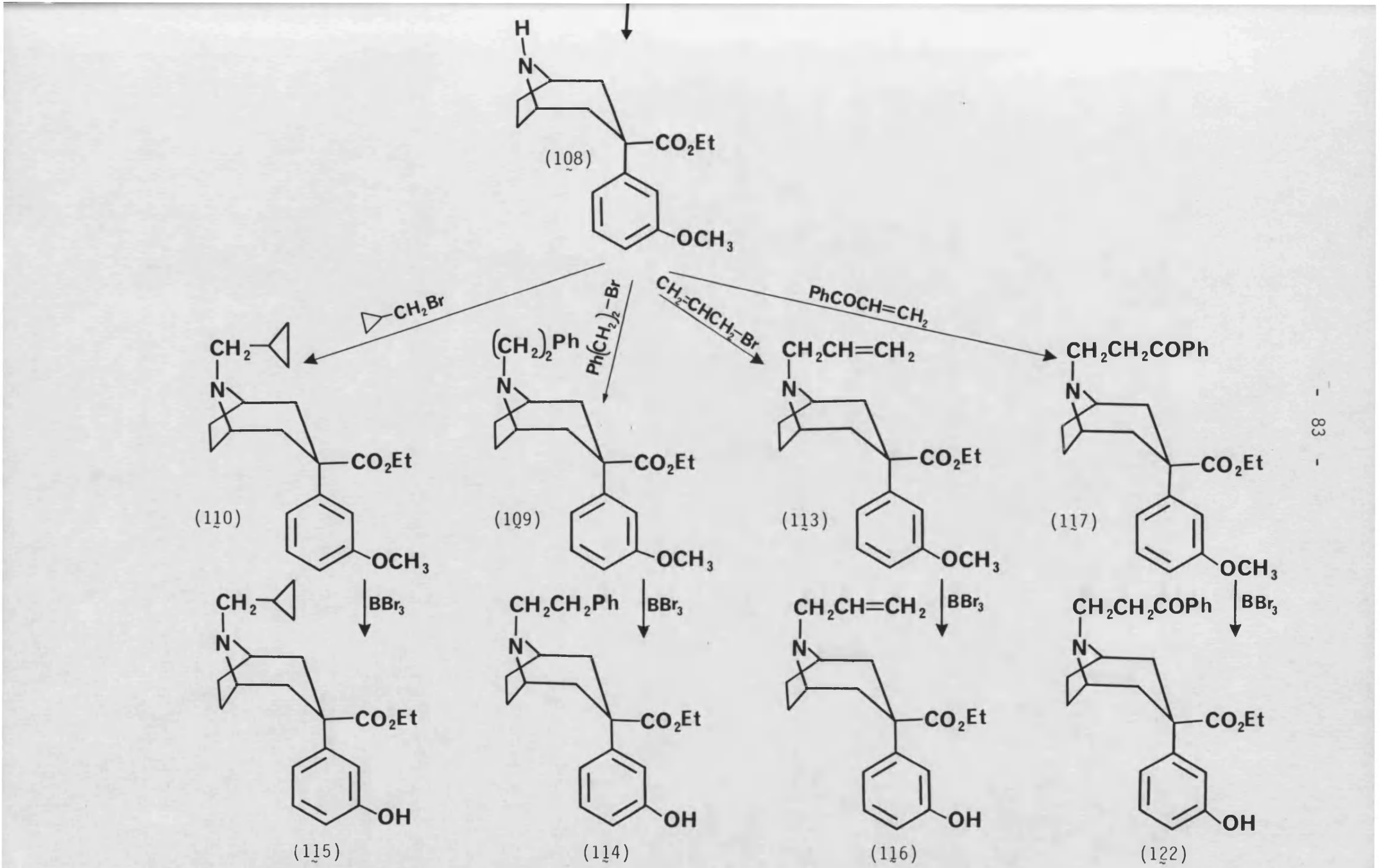
2.2.2.3 Synthesis and stereochemistry

The proposed route of synthesis for ethyl 3α-(3-hydroxyphenyl)-3β-tropane carboxylate (70) and some of its derivatives is outlined in Scheme 6.

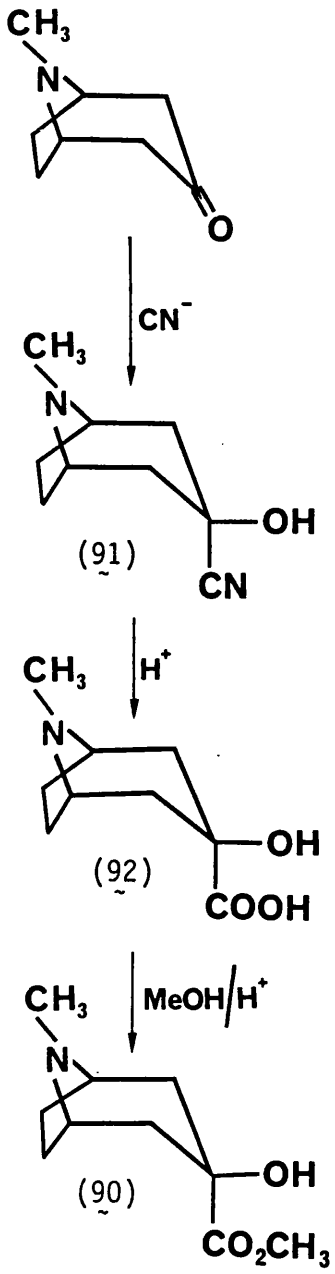
A. Ethyl 3α-(3-methoxyphenyl)-3β-tropane carboxylate

As a starting point for the synthesis of ethyl 3α-(3-methoxyphenyl)-3β-tropane carboxylate it was necessary to prepare α-ecgonine methyl ester (90)[129]. The synthetic route which successfully gave rise to the ester is shown by Scheme 7.


CH3
N
OH
CO2CH3
(90)
1. ArMgBr
2. H+
ZnCl2
(CH3CO)2O
CH3O
OCH3
(96)
O
(99)
NH2OH.HCl
Pyridine
H
Cl
(101)
HCl
CH3COOH
COOH
(103)
EtOH/H+
CO2Et
(105)
BBr3
(70)
ClCOOCH2CCl3

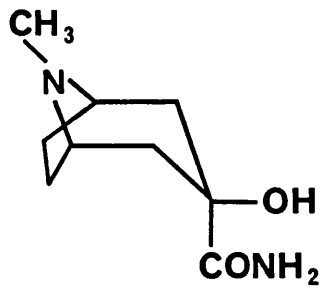

H
N
CO2Et
OCH3
(108)
CH2Br
Ph(CH2)2-Br
CH2=CHCH2-Br
PhCOCH=CH2
CH2
(CH2)2Ph
CH2CH=CH2
CH2CH2COPh
(110)
(109)
(113)
(117)
BBr3
CH2CH2Ph
OH
(115)
(114)
(116)
(122)

Scheme 6



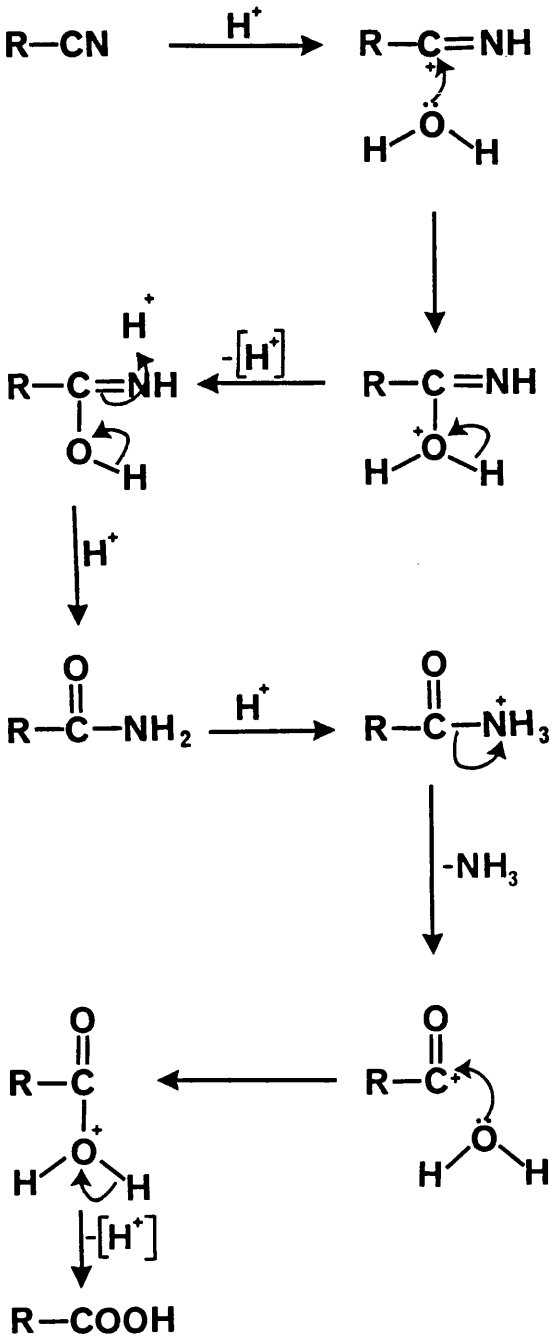
Scheme 7

An acidic solution of tropan-3-one was treated with potassium cyanide to give tropinone cyanohydrin (91). Acidic hydrolysis of this cyanohydrin afforded α-ecgonine (92), which on treatment with methanolic hydrogen chloride furnished the desired α-ecgonine methyl ester (90). Synthetic problems were encountered in the hydrolysis of tropinone cyanohydrin. Procedures recorded in the literature[129] suggested that hydrolysis could be achieved by the action of concentrated HCl for 18 hours at room temperature. However, this proved most unsatisfactory, generating mixtures of starting cyanohydrin and α-ecgonine amide (93; this amide is intermediate in the hydrolysis of the cyanohydrin to the acid - see Scheme 8). To overcome this, an IR study of the products obtained under varying conditions of temperature and time was performed, the results of which are presented in Table 8.



(93)

From this data, it was established that hydrolysis of tropinone cyanohydrin with concentrated HCl proceeded smoothly at 80°C for a period of 48 hours.


R–CN
H+
R–C=NH
H–O–H
-[H+]
H+
R–C=NH
O–H
R–C=NH
H–O–H
H+
O
R–C–NH2
H+
O
R–C–NH3
-NH3
O
R–C
O
H–O–H
O
R–C
H–O–H
-[H+]
R–COOH

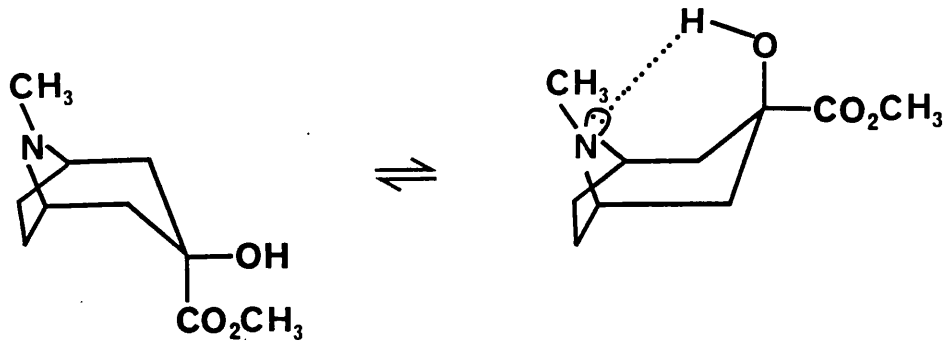
Scheme 8

Table 8 The effect of temperature and time on the hydrolysis of tropinone cyanohydrin (by concentrated HCl) to α-ecgonine

Temperature	Time	Infra Red Absorption	Assignment
Room Temp (~ 18°C)	20 hrs	No Absorption 1650-1750 cm^{-1}	Unconverted cyanohydrin
25°C	24 hrs	1690 cm^{-1} 1750 cm^{-1}	Mixture of amide (93) and acid (92)
40°C	30 hrs	1690 cm^{-1} 1750 cm^{-1}	Acid (92) and Amide (93)
80°C	6 hrs	1690-1700 cm^{-1} 1750 cm^{-1}	Acid (92) and Amide (93)
80°C	12 hrs	1700 cm^{-1} 1750 cm^{-1}	Acid (92) and Amide (93)
80°C	24 hrs	1690 cm^{-1} (weak) 1760 cm^{-1}	Acid (92) with small quantity of Amide (93)
80°C	48 hrs	1750-1760 cm^{-1}	Acid (92)

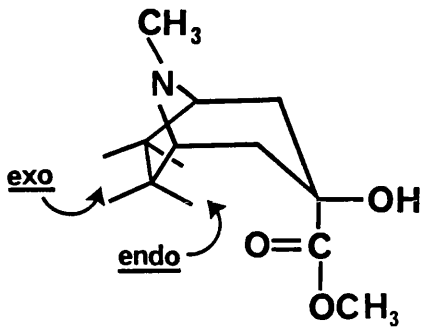
The ^{13}C-n.m.r., ^{1}H-n.m.r. and IR spectra were consistent with the assigned structure. The ^{13}C-n.m.r. spectrum (Table 14, No.1) showed sharp peak signals for the C_1C_5, C_2C_4 and C_6C_7 pairs of carbons, a characteristic that is indicative of a plane of symmetry in this compound, and a feature that all the tropane derivatives in this synthetic sequence show. The ^{1}H-n.m.r. spectrum (Table 13,

No.1) permits an analysis of the conformation of this tropane derivative to be made (the conformational analysis of this tropane derivative, and other tropanes synthesised in the course of this work, was provided by application of the principles outlined in Section 2.2.2.2, page 75). The 1(5)-H resonance at δ3.22 with $W_{\frac{1}{2}}$=16Hz suggests that the boat conformation (94) is significantly populated in $CDCl_3$. Furthermore, the O-H signal at δ5.50 is in accord with the proposed intramolecular hydrogen bonding[130]. While



(90) (94)

this evidence supports a boat conformation, a feature of the ^{1}H-n.m.r. spectrum that is diagnostic of contributions from the chair conformation is seen by examination of the signals for the 6(7)-methylene protons. The two 2-proton multiplets representing the 6(7)-methylene protons are centred near δ1.55 and 1.95 (Δ=0.4ppm). This large chemical shift difference (Δ) is indicative of a chair conformation as it suggests that the two <u>endo</u> 6(7)-H are deshielded by the carbonyl function of the ester (effect through space - 'anisotropic'[126]) to a greater extent than that experienced by the <u>exo</u> protons (see 95)[125].



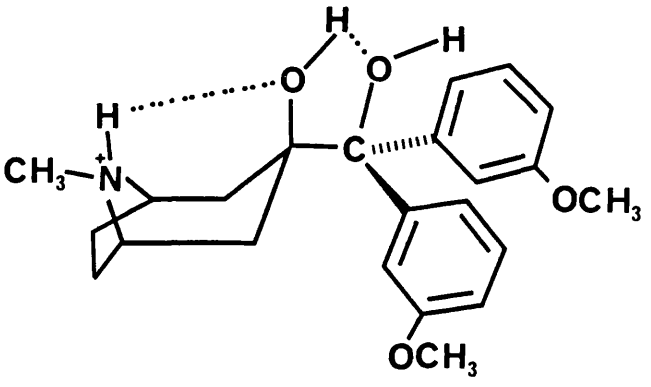
(95)

Finally, the IR spectrum showed strong intramolecular absorption at 3300 cm^{-1} indicating N····H-O bonding.

Reaction of α-ecgonine methyl ester with the Grignard reagent derived from 3-bromoanisole and magnesium afforded 3α-bis(3-methoxyphenyl)hydroxymethyl-3β-tropanol (96, Scheme 6) in high yield.

Confirmation of the structural features of this diol was achieved using ^{13}C-n.m.r. and ^{1}H-n.m.r. spectra. The ^{13}C-n.m.r. spectrum in $CDCl_3$ (Table 14, No.2) showed six lines in the aromatic region (each representing two carbons as judged by signal intensity) indicating the symmetrical nature of this molecule and of the two aromatic rings. The spectrum displayed one quaternary carbon signal in the aliphatic region instead of the expected two, a feature attributed to signal overlap, but the spectrum obtained from a sample in methanol (Table 14, No.3) revealed both quaternary carbon atoms.

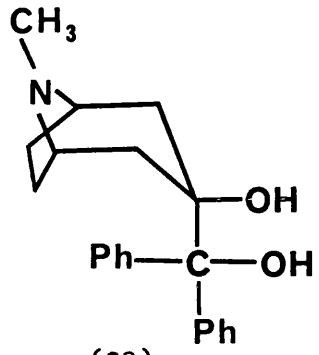
The ^{1}H-n.m.r. spectrum of the diol (96) as the hydrochloride in D_2O (Table13, No.2), displayed a 1(5)-H resonance at δ3.80 with $W_{½}$=17Hz, evidence that this tropane derivative exists in a boat conformation (97). The α-2(4)-H and β-2(4)-H signals overlapped



(97)

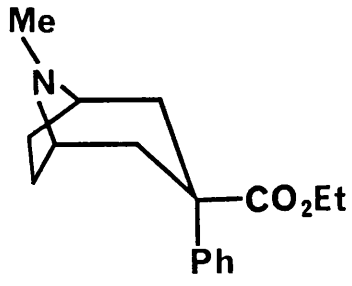
and were poorly resolved, although such a similarity in chemical shift is evidence in favour of both sets of protons being in similar environments. The 6(7)-methylene protons formed a pair of 2-proton multiplets with Δ=0.24 ppm, evidence suggesting that the exo and endo pairs of protons are in similar chemical environments, an unlikely finding if the chair contributed to the conformational equilibrium.

This evidence, supporting the boat conformation of the diol hydrochloride (97), is in accord with previous ^{13}C-n.m.r. studies of 3α-diphenylhydroxymethyl-3β-tropanol (98) and the effects of protonation[131].

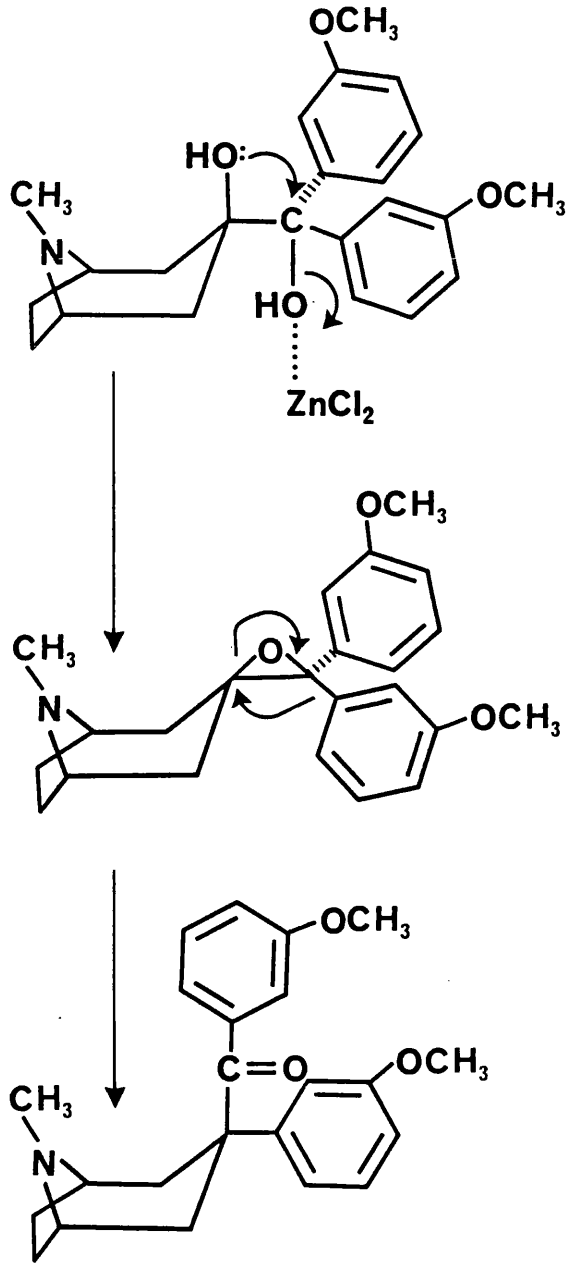


(98)

Treatment of 3α-bis(3-methoxyphenyl)hydroxymethyl-3β-tropanol hydrochloride (97) with zinc chloride and acetic anhydride yielded impure 3α-(3-methoxyphenyl)-3β-tropanyl(3-methoxyphenyl)ketone (99; Scheme 6). Mechanistically, this rearrangement is considered to proceed as outlined in Scheme 9[132]. The mechanism initially involves the catalytic formation of the β-epoxide (100) under the influence of zinc chloride. The rearrangement of the β-epoxide then proceeds with an inversion of the stereochemistry at C-3 to give the ketone (99). Evidence for the formation of the β-epoxide in this mechanism was reported by Bell and Archer[97] during studies on the synthesis of ethyl 3α-phenyl-3β-tropane carboxylate (67).



(67)

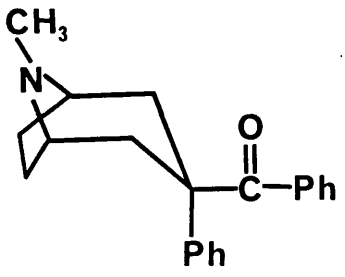


(99)

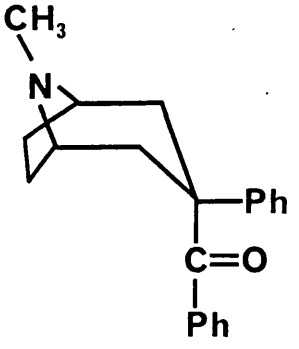
Scheme 9

Purification of the ketone at this stage was not undertaken as rapid darkening and decomposition of the oil occurred; hence it was used immediately in the synthesis of the oxime (101).

Characterisation of the ketone was based on ^{13}C-n.m.r. and IR evidence, both of which were consistent with structure. One notable feature of the ^{13}C-n.m.r. data (Table 14, No.4), which enabled the configuration of the ketone to be confirmed, was the resonating position of the C_6C_7 signal. Daum et al.[99] reported ^{13}C-n.m.r. data for the two epimeric tropane derivatives (89) and (102). The chemical shift for the C_6C_7 carbons in these two epimers differed considerably : 29.2 ppm for (89) and 24.4 ppm for (102).



(89)



(102)

In the ketone (99), the C_6C_7 resonating position was 29.04 ppm. This chemical shift correlates well with the configuration displayed by (89).

Synthesis of the oxime (101):

The synthesis of the oxime (101) was effected by treatment of 3α-(3-methoxyphenyl)-3β-tropanyl(3-methoxyphenyl)ketone (99) with hydroxylamine hydrochloride in propan-1-ol and pyridine (Scheme 6). Pyridine is used in this reaction to liberate the reactive free hydroxylamine by forming pyridine hydrochloride. The forcing conditions of this reaction that were necessary to effect oxime formation were associated with steric hindrance impeding access of hydroxylamine to the reactive C=O.

The ^{1}H-n.m.r., ^{13}C-n.m.r. and IR spectra of the oxime were consistent with structure (101). The ^{1}H-n.m.r. spectrum (base in $CDCl_3$; Table 13, No.3) provided clear evidence of the preferred conformation of this tropane derivative. The 1(5)-H resonance at δ3.22 with $W_{½}$=11Hz supports the chair form as the favoured conformation. The α- and β- 2(4)-H signals were well resolved and showed very small vicinal coupling, a finding also in accord with a chair conformation. Both signals were to low field of the N-methyl resonance, a feature attributed to deshielding of the α-2(4)-H by an axial aromatic ring[133], and the β-2(4)-H by the C=N. The 6(7)-methylene hydrogens formed two 2-proton multiplets centred at δ1.34 and 1.65. The chemical shift difference (Δ0.31 ppm) is indicative of a shielding effect experienced by the endo hydrogens due to an axially orientated aromatic system[127]. This shielding effect is exerted when the plane of the aromatic ring is at right angles to a plane passing through nitrogen and C-3 of the piperidine ring[128]. This shielding effect would be absent if the oxime existed in a boat conformation.

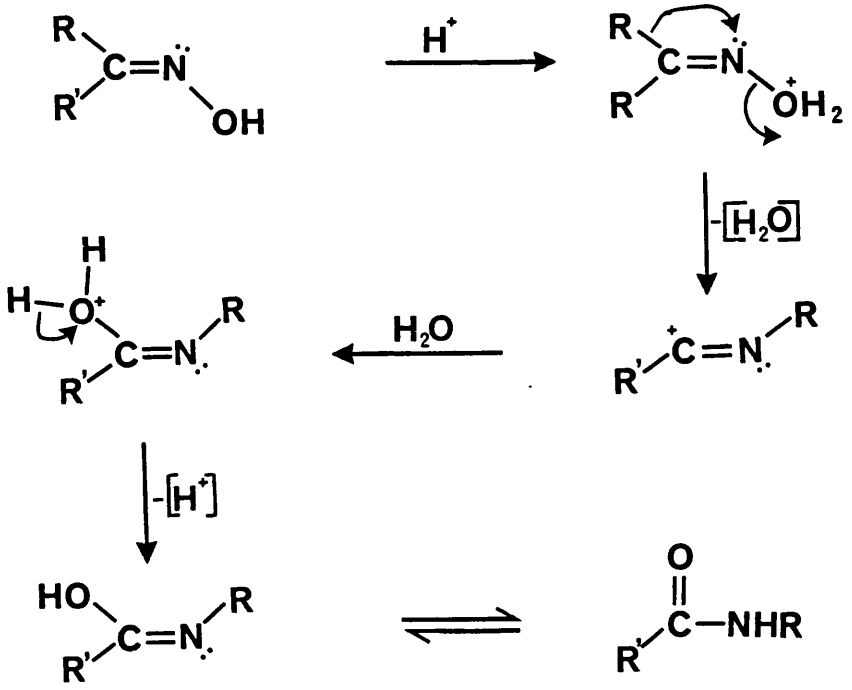
One notable characteristic of the ^{13}C-n.m.r. spectrum (Table 14, No.5) was the presence of a signal at δ162.7 ppm, attributed to the oxime C=N. This was assigned with the aid of the INEPT programme and chemical shift correlations and compares with the C=O shift at δ173.2 ppm in the starting material.

The IR spectrum of (101) showed strong absorption at 3100-3500 cm^{-1} for the hydroxyl group and the complete absence of absorption at 1780 cm^{-1}, this latter being a feature associated with the starting ketone.

Beckmann rearrangement of the oxime (101):
The Beckman rearrangement[134], a general reaction of oximes, consists of the conversion of an oxime into an amide.

$$RR'C{=}N{-}OH \longrightarrow R{-}CONHR' + R'{-}CONHR$$

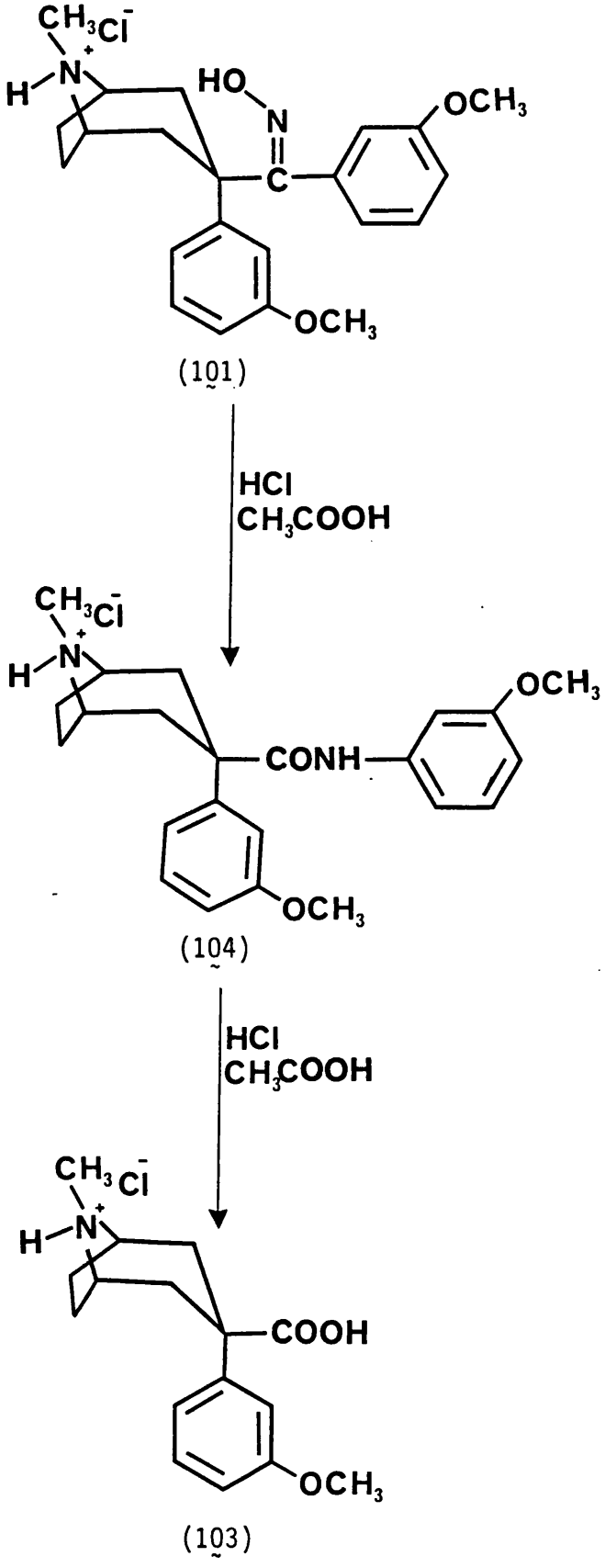
The reaction is catalysed by a wide variety of acidic reagents including H_2SO_4, $SOCl_2$, PCl_5, BF_3 and $HCl|CH_3COOH$. The rearrangement, outlined mechanistically in Scheme 10, involves alkyl migration to an electron deficient nitrogen formed by loss of



Scheme 10

water from the protonated oxime. The initially formed cation reacts with water to give the enol form of an amide, which then reverts to the amide proper. The Beckmann rearrangement is a stereospecific reaction, the group that migrates being the one which is trans (anti) to the hydroxy group in the oxime (R in Scheme 10)[135].

When the oxime (101) was subjected to the action of hydrogen chloride in hot acetic acid it was converted directly to 3α-(3-methoxyphenyl)-3β-tropane carboxylic acid hydrochloride (103) in good yield. The anilide (104), the expected product of the Beckmann rearrangement, was cleaved under these circumstances to yield the above named carboxylic acid (Scheme 11).



(101)

(104)

(103)

Scheme 11

The ^{1}H-n.m.r. spectrum of this acid (1Q3; Table 13, No.4) was consistent with the structure assigned and allowed analysis of the conformation and relative configuration of this tropane derivative to be made. The 1(5)-H resonance at δ3.93 with $W_{\frac{1}{2}}$=11Hz supported the chair as the preferred conformation. The α- and β-2(4)-H protons showed small vicinal coupling as expected for this conformation. Analysis of the resonance signals for the exo and endo 6(7)-methylene protons at δ1.89 and 1.59 respectively (Δ=0.3 ppm) indicated enhanced shielding of the endo protons by an axially orientated aromatic system[127].

The IR and ^{13}C-n.m.r. were also consistent with structure. Thus, the IR spectrum showed carbonyl absorption at 1730 cm^{-1}, a feature associated with carboxylic acids, while complete absence of absorption in the range 1630-1680 cm^{-1} (anticipated carbonyl absorption of a secondary amide) verified that hydrolysis of the intermediate amide had occurred. The ^{13}C-n.m.r. spectrum (Table 14, No.6) displayed only seven signals in the aromatic region, which was indicative of one aromatic ring (and C=O) and evidence of hydrolysis of the amide occurring.

Esterification of the carboxylic acid (1Q3) with ethanolic hydrogen chloride furnished ethyl 3α-(3-methoxyphenyl)-3β-tropane carboxylate hydrochloride (1Q5; Scheme 6). The ^{1}H-n.m.r., ^{13}C-n.m.r. and IR spectra of this ester were consistent with structure, and the ^{1}H- and ^{13}C-n.m.r. provided evidence relating to the stereochemical features of (1Q5).

As this ester is a key compound in the synthesis of the phenolic tropane analogues, attention will be given to the stereochemical and structural features associated with it.

The ^{1}H-n.m.r. spectrum of the ester as the base in $CDCl_3$ (Table 13, No.5) suggested that the boat conformation (106) was significantly populated. The 1(5)-H resonance at δ3.19 and with $W_{\frac{1}{2}}$=16Hz supported this deduction. The resonance of the β-2(4)-H centred at δ3.06 displayed vicinal coupling in the range 7-8Hz, indicative of a degree of eclipsing of the β-2(4)-H and the 1(5)-H protons. The α-2(4)-H, centred at δ1.81, displayed geminal coupling only, as vicinal coupling was too small to measure, see Fig.8.

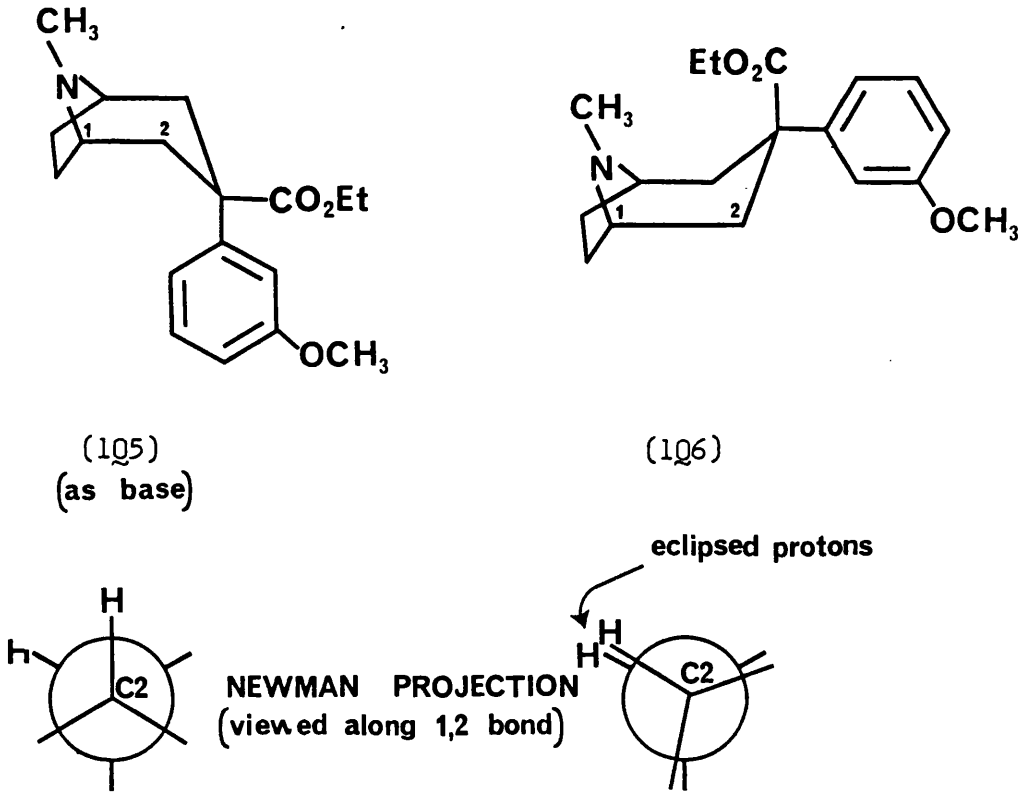


Figure 8

The large chemical shift difference between the α- and β- 2(4)-H protons is attributed to deshielding of the β-protons by the carbonyl of the ester group[125]. The exo and endo 6(7)-H signals were separated at δ1.38 and 1.96 respectively (Δ=0.58 ppm), a feature diagnostic of some contribution of the chair conformation (105); that is, endo protons are shielded to a greater extent than exo protons as a result of an axial aromatic system (see discussion on oxime; page 94)[127]. In addition, this finding confirms the relative configuration of the ester (see ^{13}C-n.m.r. discussion).

At this point, confirmation of the substitution pattern in the aromatic ring is possible. The rearrangement of the diol hydrochloride (97) to the ketone (99; page 91) assumed that the transfer of the aromatic ring from C-OH to C-3 maintains a meta substitution pattern. Figure 9 illustrates the evidence in support of this meta substitution pattern in the aromatic ring based on a consideration of the coupling pattern experienced by the protons H_A, H_B, H_C and H_D.

^{13}C-n.m.r. evidence in support of the axial aromatic system was provided by the C_6C_7 carbon resonance (Table 14, No.7). Data on the two epimeric tropane analogues (67) and (107) of pethidine has been reported[99], and a significant difference in the C_6C_7 resonance noted. The ester (105) displayed a C_6C_7 resonance at δ27.63 ppm and hence the assigned configuration involving an axial aromatic ring is substantiated.

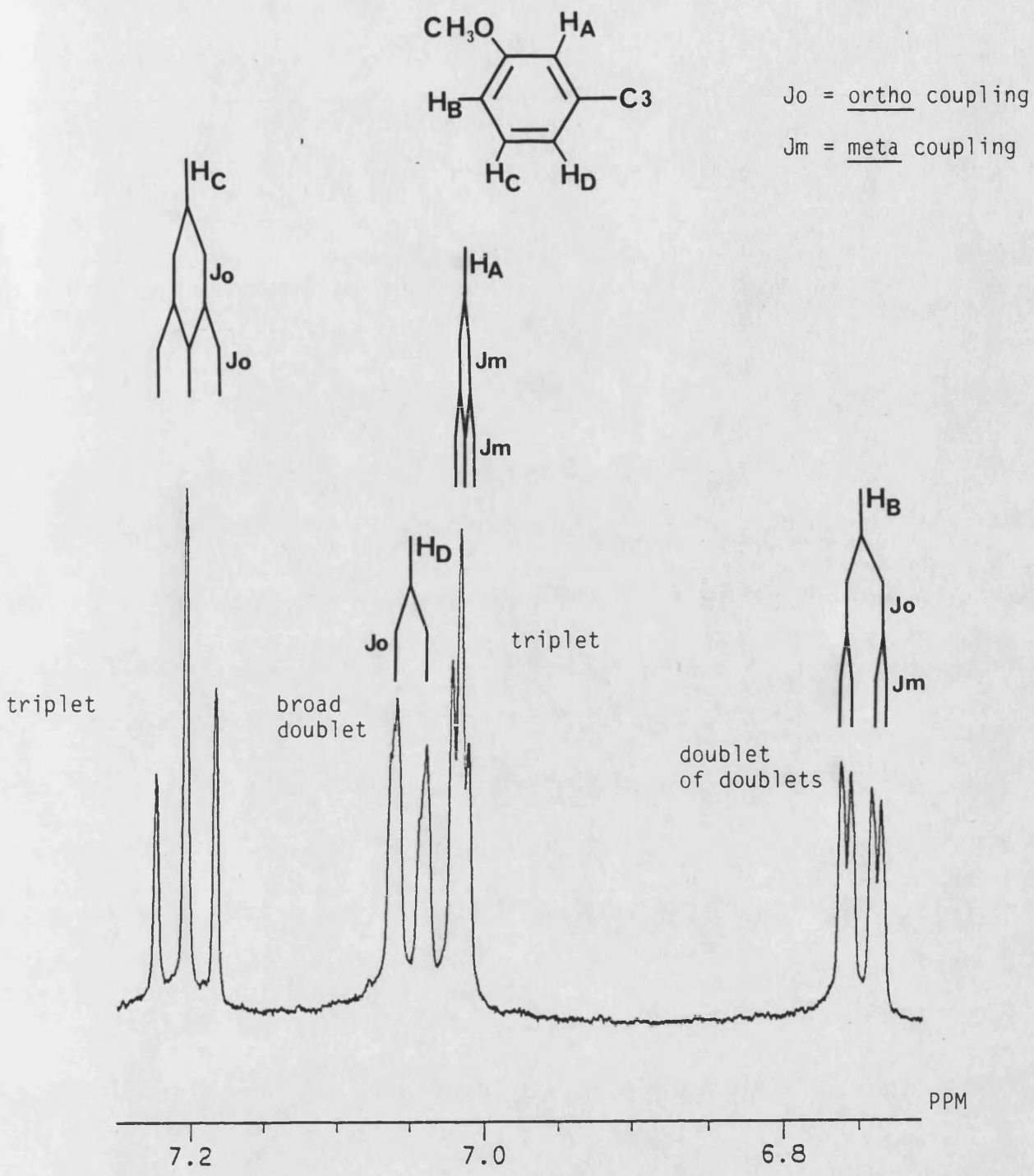
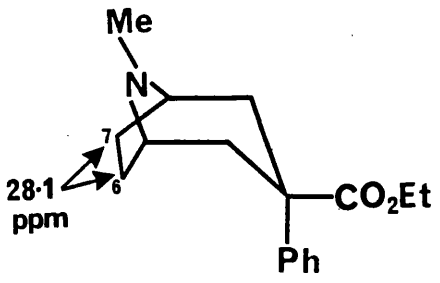
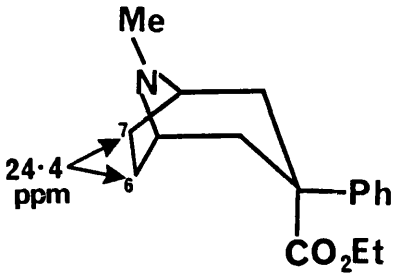


Figure 9 Partial ^{1}H-n.m.r. spectrum (at 270 MHz) to illustrate coupling pattern of aromatic protons in ethyl 3α-(3-methoxyphenyl)-3β-tropane carboxylate



(67)



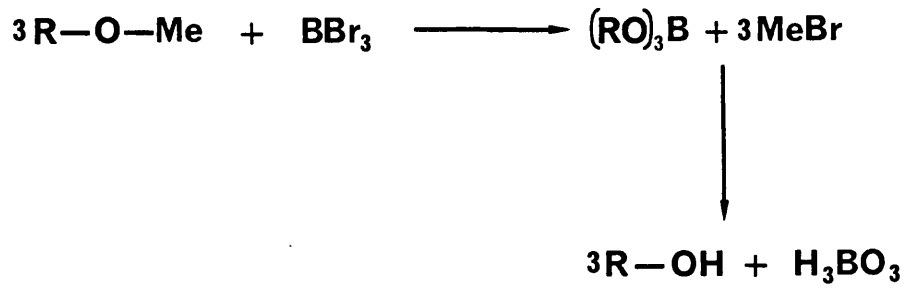
(107)

B. Synthesis of ethyl 3α-(3-hydroxyphenyl)-3β-tropane carboxylate (70) by O-demethylation

The synthesis of the phenolic tertiary amine (70; Scheme 6), one of the main aims of this present work, was achieved by O-demethylation of ethyl 3α-(3-methoxyphenyl)-3β-tropane carboxylate with boron tribromide[136].

Acid halides and anhydrides in the presence of metallic halides as catalysts have been used to effect ether cleavage[137]. Boron chloride, however, has been shown to cleave ethers even in the absence of acid halides and anhydrides[138]. The marked ability of boron halides to form complexes with ethers, and the ease with which etherates with boron chloride disproportionate, led to the assumption that boron tribromide might prove a suitable reagent for cleaving ethers. Studies have shown this to be the case[136], with the results indicating that no mixtures of products were produced in the course of the ether cleavage. The reaction is considered as

proceeding in two steps[139] as outlined in Scheme 12, and has been used in the O-demethylation of codeine to morphine[140].



Scheme 12

The O-demethylation of the tertiary amine (105) proceeded smoothly yielding ethyl 3α-(3-hydroxyphenyl)-3β-tropane carboxylate (70) as a clean product in poor yield.

The spectral data obtained for this phenolic tropane derivative was consistent with its assigned structure. Thus, the ^{13}C-n.m.r. showed absence of an O-CH_3 signal, and the IR spectrum showed strong absorption at 3300 cm $^{-1}$ associated with the presence of the phenolic OH.

The ^{1}H-n.m.r. spectrum was consistent with structure and provided evidence of the stereochemical features of this tropane derivative. The base in $CDCl_3$ (Table 13, No.6) displayed a 1(5)-H signal at δ3.23 with $W_{\frac{1}{2}}$=12Hz, evidence supporting the chair as the most significantly populated conformer. The exo and endo 6(7)-methylene

protons were well separated (Δ=0.44 ppm) in accord with an axial aromatic ring exerting a shielding effect on the endo protons[127].

The ^{1}H-n.m.r. spectrum of this tropane derivative hydrochloride in D_2O also confirmed the chair as the favoured conformation. The 1(5)-H resonance fell near the higher field lines of the $OC\underline{H}_2CH_3$ quartet, but was sufficiently resolved at 400MHz to permit the measurement of $W_{\frac{1}{2}}$=8Hz. Examination of the resonance signals for the α- and β- 2(4)-H indicated that no large vicinal coupling was present, further support of the chair conformation.

C. Synthesis of ethyl 3α-(3-methoxyphenyl)-3β-nortropane carboxylate (108) by N-dealkylation

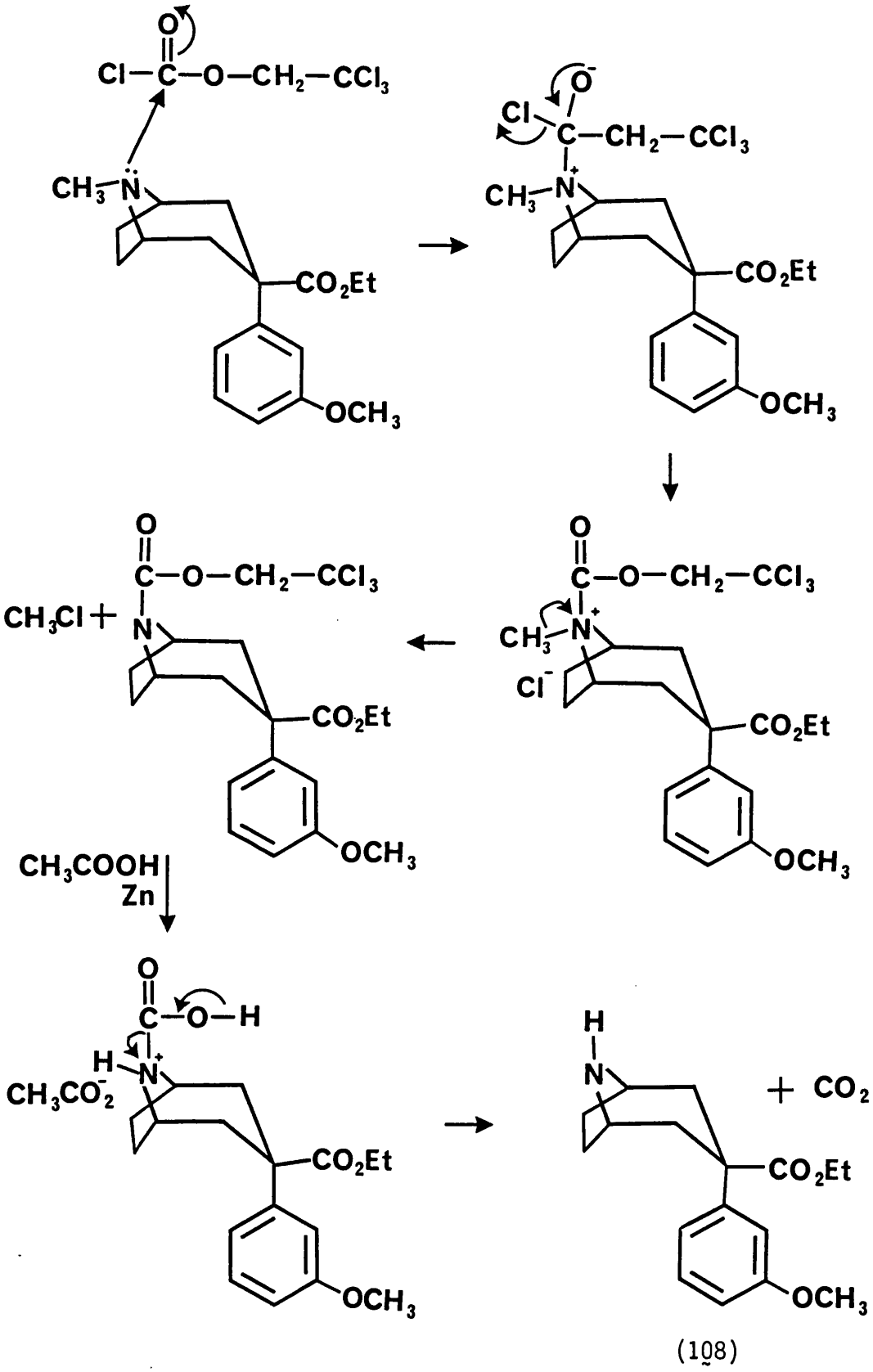
In this work, the secondary amine (108; Scheme 6), a key compound in the synthesis of a whole series of N-alkylated 3α-(3-methoxyphenyl)-3β-nortropane carboxylates and their corresponding phenolic analogues, was obtained by N-demethylation of the tertiary amine (105) with 2,2,2-trichloroethylchloroformate[141].

Chloroformate esters, such as ethyl[142], phenyl[143] and vinyl[144,145], have been used for N-demethylations and have been reported to give good yields and clean products. However, the use of these reagents is limited as the intermediate carbamates produced during the reaction are resistant to hydrolysis and demand long periods of reflux with strong acids or bases to yield the corresponding secondary amine, conditions not tolerated by acid or base labile compounds[141]. The use of 2,2,2-trichloroethylchloroformate overcomes this problem as the intermediate carbamate formed

undergoes facile hydrolysis at room temperature in the presence of zinc and acetic acid. Mechanistically the reaction is outlined in Scheme 13.

The N-demethylation of ethyl 3α-(3-methoxyphenyl)-3β-tropane carboxylate proceeded smoothly yielding the corresponding secondary amine (108) in good yield.

The ^{1}H-n.m.r. and ^{13}C-n.m.r. spectra of the resulting secondary amine were consistent with structure, both showing absence of an N-methyl signal. The ^{1}H-n.m.r. data (Table 15, No.1) displayed characteristic features associated with the chair form being the most significantly populated in this nortropane. Thus, the 1(5)-H signal at δ4.21 with $W_{\frac{1}{2}}$=11.5Hz is evidence of small vicinal coupling with the 2(4)-H protons and, additionally, the α-2(4)-H and β-2(4)-H resonances at δ2.96 and 2.82 respectively only showed large geminal coupling. The chemical shift difference of the α-and β-2(4)-H was small, indicative of deshielding being exerted on both sets of protons (α-H deshielded by axial aromatic system[133], β-H deshielded by $\overset{+}{N}H$ and CO_2Et[125]). Furthermore, the exo and endo 6(7)-methylene protons were well separated (Δ=0.37 ppm), evidence to substantiate an axial aromatic ring (as a result of an enhanced shielding effect on endo protons)[127].

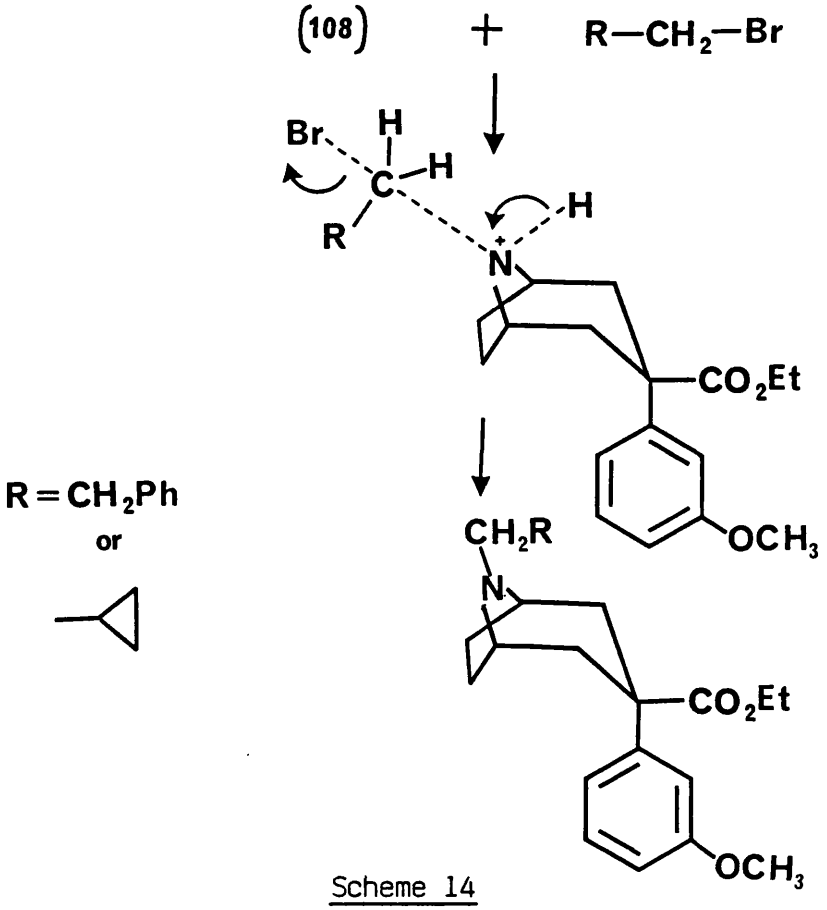


(108)

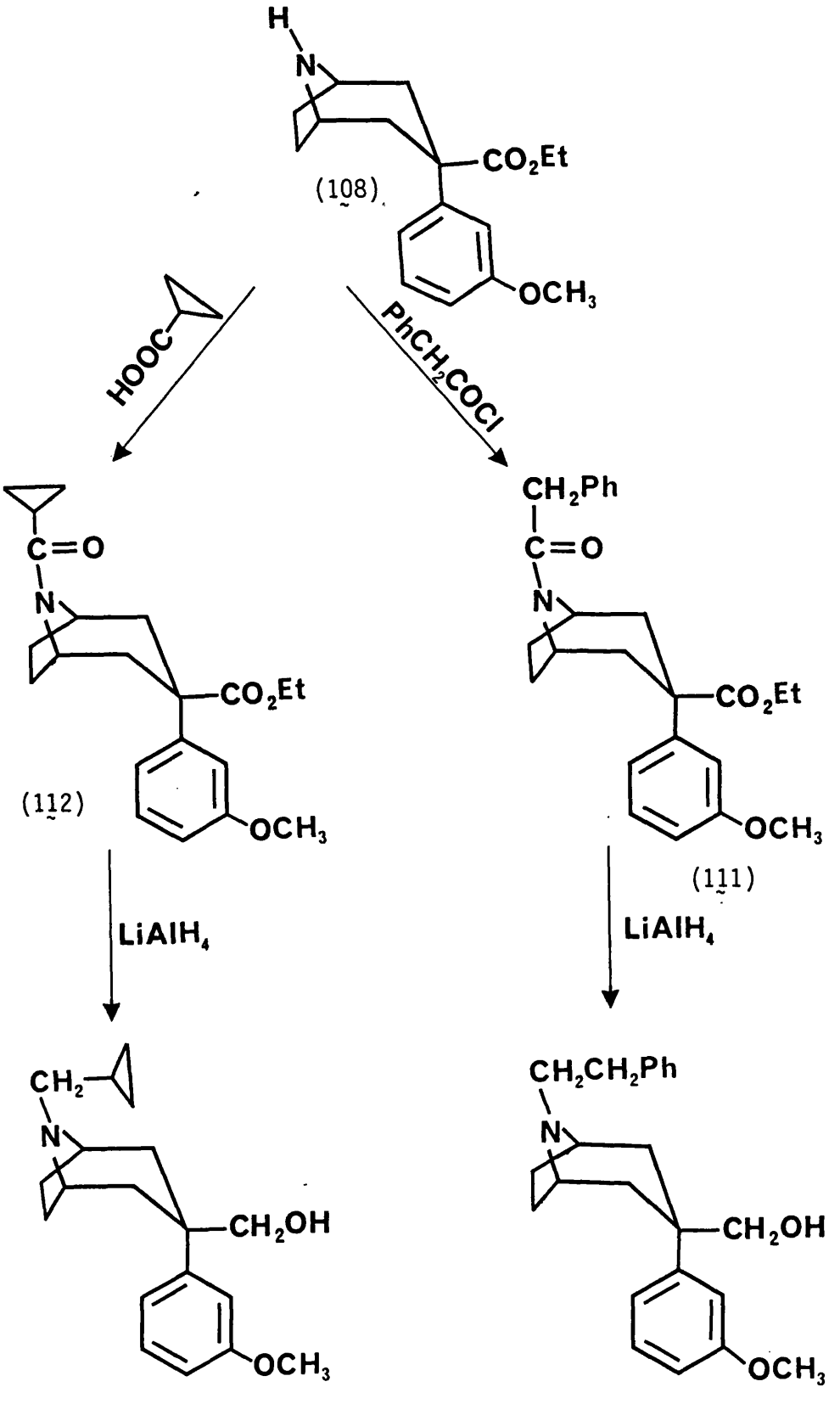
Scheme 13

D. Synthesis of ethyl N-allyl-3α-(3-methoxyphenyl)-3β-nortropane carboxylate (113), ethyl N-(cyclopropylmethyl)-3α-(3-methoxyphenyl)-3β-nortropane carboxylate (110), ethyl 3α-(3-methoxyphenyl)-N-phenethyl-3β-nortropane carboxylate (109) and their phenolic analogues

The synthesis of the two tropane derivatives (109) and (110; Scheme 6) was achieved by direct alkylation of the secondary amine (108) with the appropriate alkyl halide. This alkylation is of the nucleophilic category proceeding via an S_N2 mechanism as outlined in Scheme 14[146].



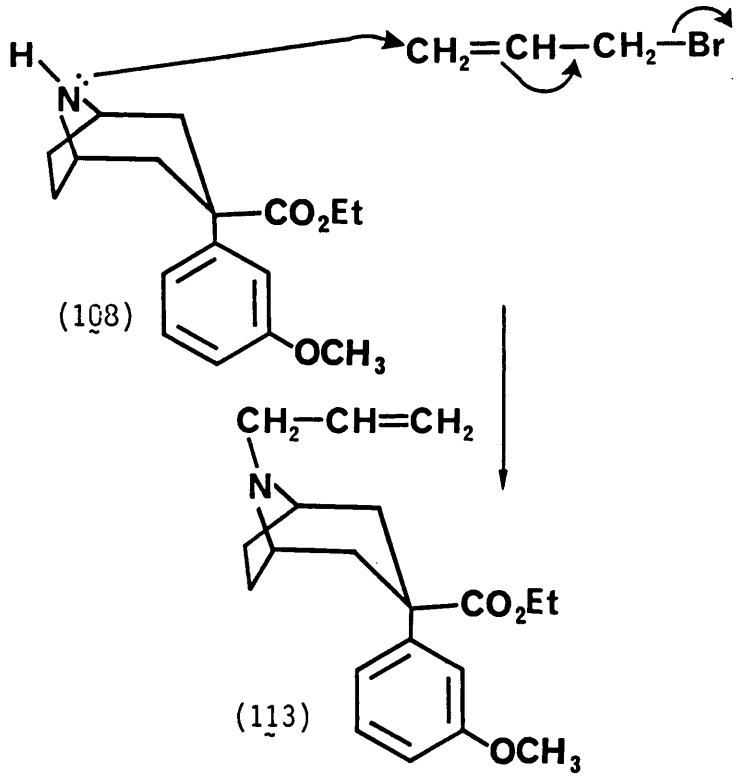
Scheme 14


H
N
CO2Et
OCH3
(108)
HOOC
PhCH2COCl
C=O
CH2Ph
(112)
(111)
LiAlH4
CH2
CH2OH
CH2CH2Ph

Scheme 15

It was fortuitous that the use of phenethyl bromide and cyclopropylmethyl bromide succeeded in generating the two required tertiary amines (109) and (110). The alternative method for the introduction of such N-alkyl groups involves the synthesis of the amides (111) and (112) by reaction with phenacetyl chloride or cyclopropane carboxylic acid respectively, followed by $LiAlH_4$ reduction to the amine. Such an approach would not be tolerated in this synthetic series as concomitant reduction of the 3β-carboethoxy group would occur (Scheme 15).

Reaction of the secondary amine (108) with allyl bromide afforded (113). Owing to possible allylic rearrangements of allyl bromide, the nucleophile (108) may attack the γ-carbon instead of the usual α-carbon via a S_N2' mechanism[147] (Scheme 16).



(108)

(113)

Scheme 16

It is suggested that this S_N2' mechanism is more appropriate than the conventional S_N2 mechanism when bulky nucleophiles are employed, since the steric hindrance at the γ-carbon is considerably less than at the α-carbon.

Characterisation of these three derivatives was based on the spectral data obtained. The ^{13}C-n.m.r., ^{1}H-n.m.r. and IR spectra were consistent with the assigned structures and notably the ^{13}C-n.m.r. spectra displayed carbon signals for the appropriate N-alkyl group (Table 16, Nos. 2, 4, 6).

The ^{1}H-n.m.r. data provided evidence in relation to the stereochemical features associated with these three tropane derivatives (Table 15, Nos. 2, 4, 6). Examination of the 1(5)-H resonance signal indicated that the three tropane derivatives existed in the chair conformation. The $W_{\frac{1}{2}}$ value was within the range 10 to 13Hz signifying that vicinal coupling with the 2(4)-H protons was small. Furthermore, the resonance of the exo and endo 6(7)-methylene protons in all three derivatives were well separated in accord with a chair conformation.

O-Demethylation of the three N-alkylated nortropanes (109), (110) and (113) with boron tribromide[136] yielded the corresponding phenolic analogues (114), (115) and (116; Scheme 6). The yield of these phenolic tropane derivatives was poor, a finding experienced in the O-demethylation of the tropane (105; page 102). The ^{13}C-n.m.r. and ^{1}H-n.m.r. of these three derivatives was consistent with structure, the notable feature being absence of the signal for the

O-CH_3.

The chair conformation can be assigned to all three derivatives on the basis of ^{1}H-n.m.r., with $W_{\frac{1}{2}}$ of the 1(5)-H resonance being in the range 10 to 12Hz. Other features of the ^{1}H-n.m.r. spectra were consistent with this conformation.

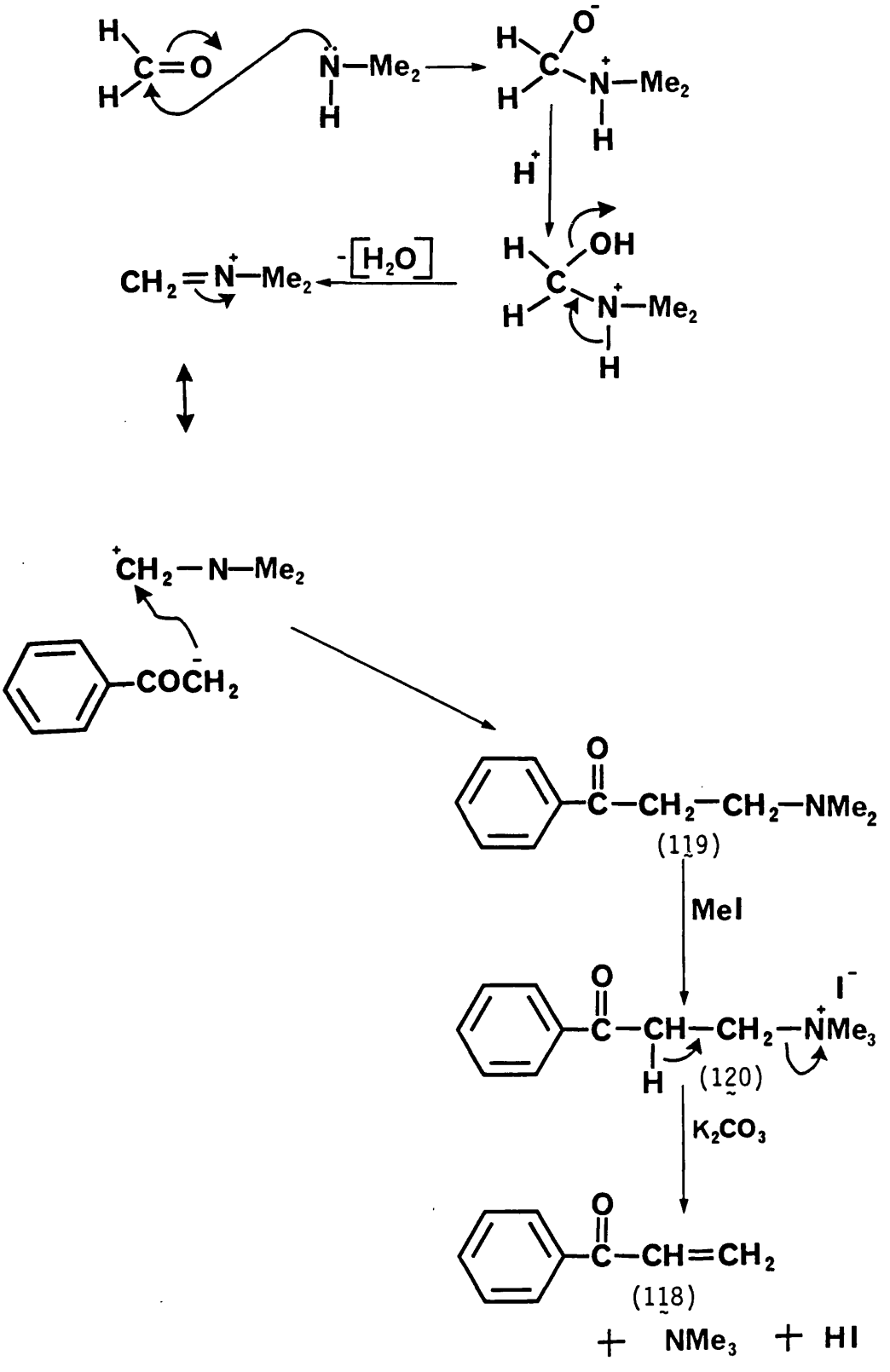
E. Synthesis of ethyl N-(2-benzoylethyl)-3α-(3-methoxyphenyl)-3β-nortropane carboxylate and its phenolic analogue

The synthesis of ethyl N-(2-benzoylethyl)-3α-(3-methoxyphenyl)-3β-nortropane carboxylate (117; Scheme 6) was achieved by a Michael reaction[148-150] of the secondary amine (108) with phenyl vinyl ketone (118).

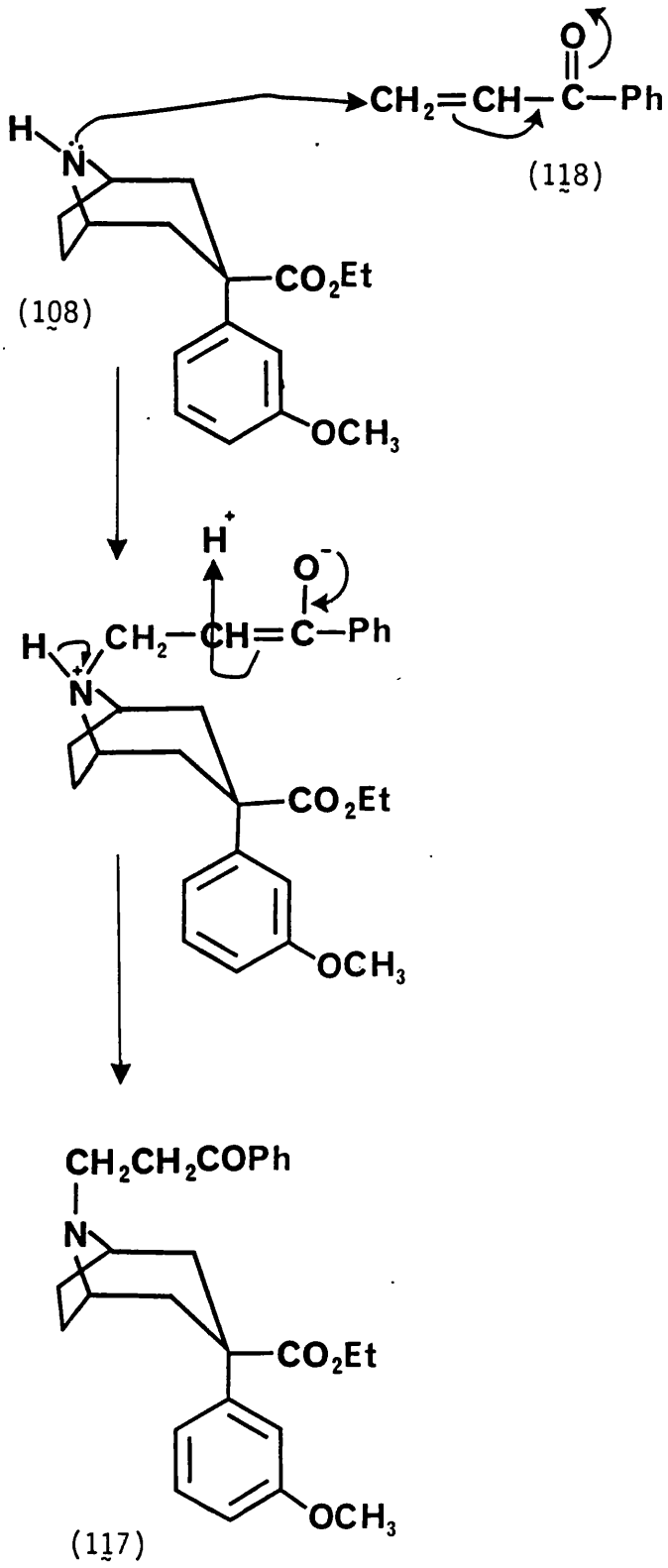
Phenyl vinyl ketone was prepared by the Mannich reaction[151] of dimethylamine hydrochloride, acetophenone and paraformaldehyde to form the base (119), followed by quaternisation with methyl iodide to give the quaternary salt (120). Hofmann elimination[152] of (120) with K_2CO_3 solution afforded the required ketone (118; Scheme 17).

The Michael addition of the secondary amine (108) and phenyl vinyl ketone proceeded smoothly to yield the adduct (117) in reasonable yield. This Michael addition is of the nucleophilic category, the mechanism of which is outlined in Scheme 18.

Confirmation of the structure was based on ^{13}C-n.m.r. and ^{1}H-n.m.r. evidence. The ^{13}C-n.m.r. spectrum (Table 16, No.8) displayed the


H
C=O
H
N–Me2
H
H
C
O
N–Me2
H
H+
H
C
OH
N–Me2
H
H
-[H2O]
CH2=N–Me2
CH2–N–Me2
COCH2
O
C–CH2–CH2–NMe2
(119)
MeI
O
C–CH–CH2–NMe3
I-
H
(120)
K2CO3
O
C–CH=CH2
(118)
+ NMe3 + HI

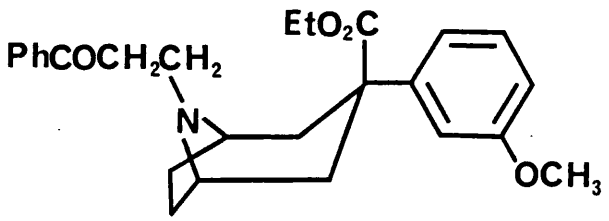
Scheme 17



Scheme 18

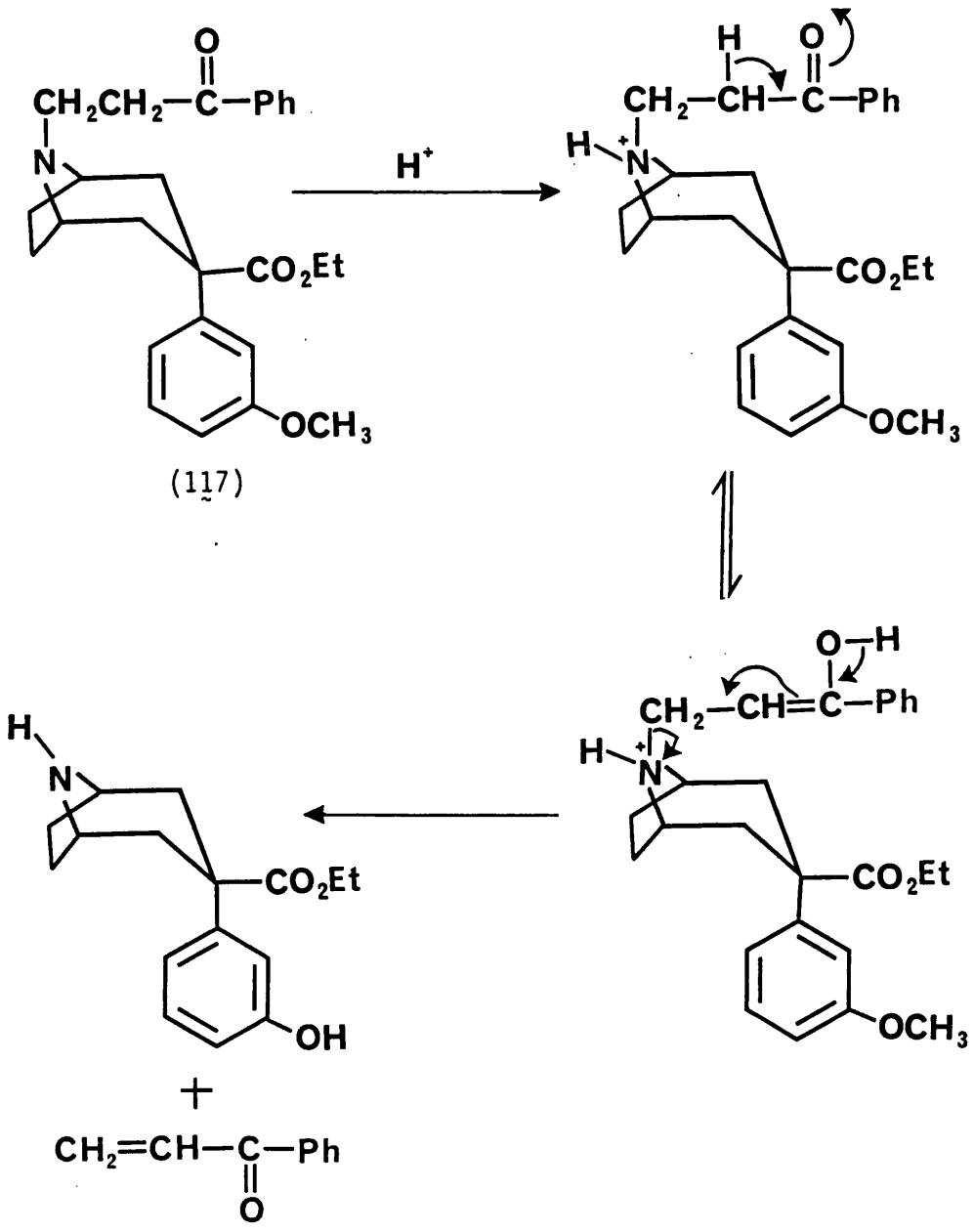
correct number of carbon resonances and, notably, two carbonyl signals at δ199.1 and 175.2 for the ketone and ester C=O group respectively.

The ^{1}H-n.m.r. spectrum (Table 15, No.8) in $CDCl_3$ was consistent with the assigned structure and provided evidence in relation to the conformational preference of this tropane derivative. The 1(5)-H resonance at δ3.35 with $W_{\frac{1}{2}}$=16Hz is indicative of a high population of the boat conformation (121), a finding substantiated by the small difference in the chemical shifts of the exo and endo 6(7)-methylene protons (Δ=0.2 ppm).



(121)

An attempted synthesis of N-(2-benzoylethyl)-3α-(3-hydroxyphenyl)-3β-nortropane carboxylate (122) by O-demethylation with BBr_3[136] at room temperature failed, yielding only an intractible oil. The most probable reason for the failure of this reaction is due to a reverse Michael reaction[149] (reverse of the Michael addition) catalysed by the acidic nature of the BBr_3 (see Scheme 19).

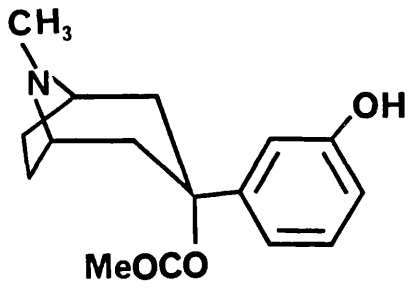


(117)

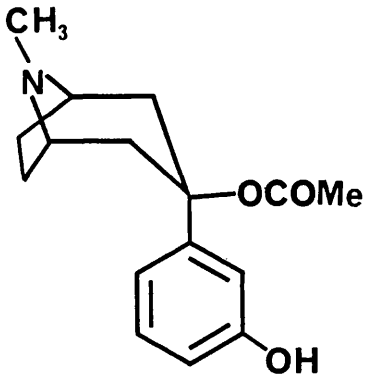
Scheme 19

2.2.3 Synthetic and stereochemical studies of other tropane derivatives

The synthesis of the two esters (123) and (124) was a further objective of the present work.



(123)

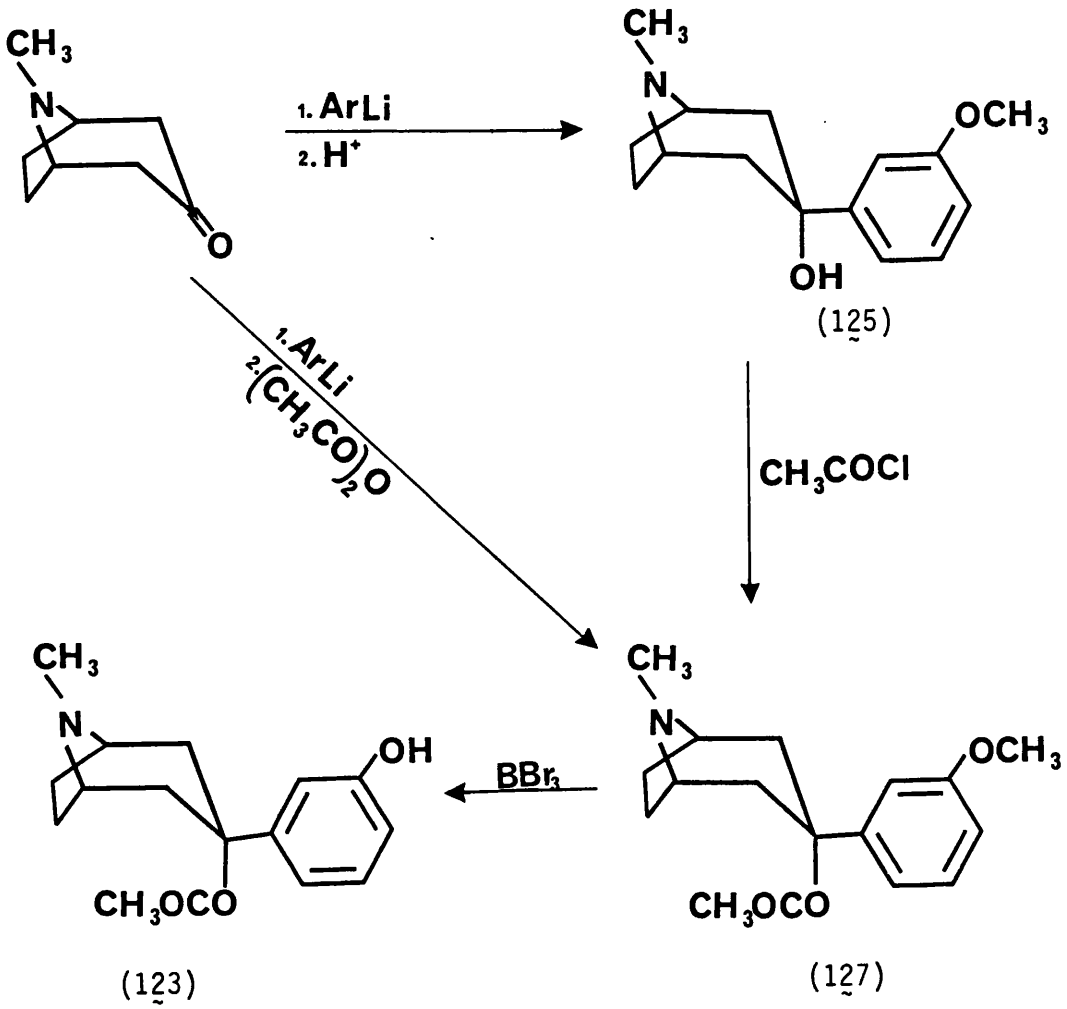


(124)

2.2.3.1 The attempted synthesis of 3α-acetyloxy-3β-(3-hydroxyphenyl)tropane (123)

The proposed route of synthesis for this tropane derivative is outlined in Scheme 20.

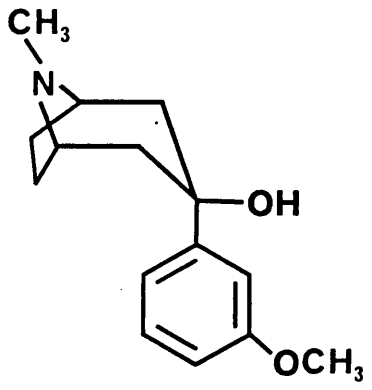
The alcohol (125) was synthesised by the condensation of 3-anisyl lithium (derived from 3-bromoanisole and n-butyl lithium) with tropan-3-one. The reaction proceeded smoothly yielding an oil, which by t.l.c. analysis was shown to be a mixture of starting ketone and the desired product. Separation of this mixture was achieved by trituration with ether, the alcohol separating as a white solid.


CH3
N
O
1. ArLi
2. H+
OCH3
OH
(125)
1. ArLi
2. (CH3CO)2O
CH3COCl
OH
BBr3
CH3OCO
(123)
(127)

Scheme 20

Structural and stereochemical features of this tropan-3-ol (125) were deduced by analysis of the ^{13}C-n.m.r., ^{1}H-n.m.r. and IR spectra.

The reaction is considered to be stereospecific with complete absence of production of the epimer (126). This is shown by ^{1}H-n.m.r. and ^{13}C-n.m.r. analysis.



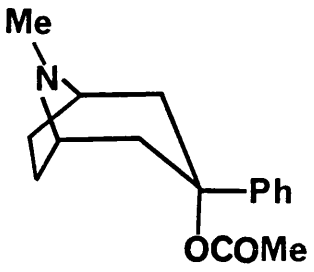
(126)

The stereochemical features of this alcohol is verified by analysis of the ^{1}H-n.m.r. spectrum (Table 18, No.6). The two 2-proton multiplets of the exo and endo 6(7)-methylene protons were well separated. This is attributed to deshielding of the endo protons by an axially orientated hydroxyl group[124]. Evidence that this tropane derivative exists in a chair conformation is based on analysis of the 1(5)-H signal. Resonating at δ3.21 with $W_{\frac{1}{2}}$=9Hz, it indicates small vicinal coupling with the 2(4)-protons, as expected for such a conformation.

The ^{13}C-n.m.r. (Table 19, No.6) was consistent with structure, notable features of the spectrum being the disappearance of the C=O resonance (characteristic of the starting ketone) and the appearance of the appropriate aromatic signals.

Having succeeded in the production of the alcohol (125), attention was then given to the synthesis of the ester (127). This tertiary alcohol proved resistant to esterification. The use of nucleophilic catalysts such as pyridine[153], triethylamine[154] and p-toluenesulphonic acid[155] (reagents known to promote the esterification of tertiary alcohols) failed to generate the desired ester, and usually resulted in the formation of olefinic and other unidentifiable products.

Attempts to effect esterification using the *in situ* method described by Casy and Beckett[47] also failed, and generated the alcohol(125) only. This facile *in situ* method involved the addition of acetic anhydride directly to the lithium complex derived from the reaction of tropan-3-one and 3-anisyl lithium. (The synthesis of the ester (59) was achieved by adopting a similar procedure).



(59)

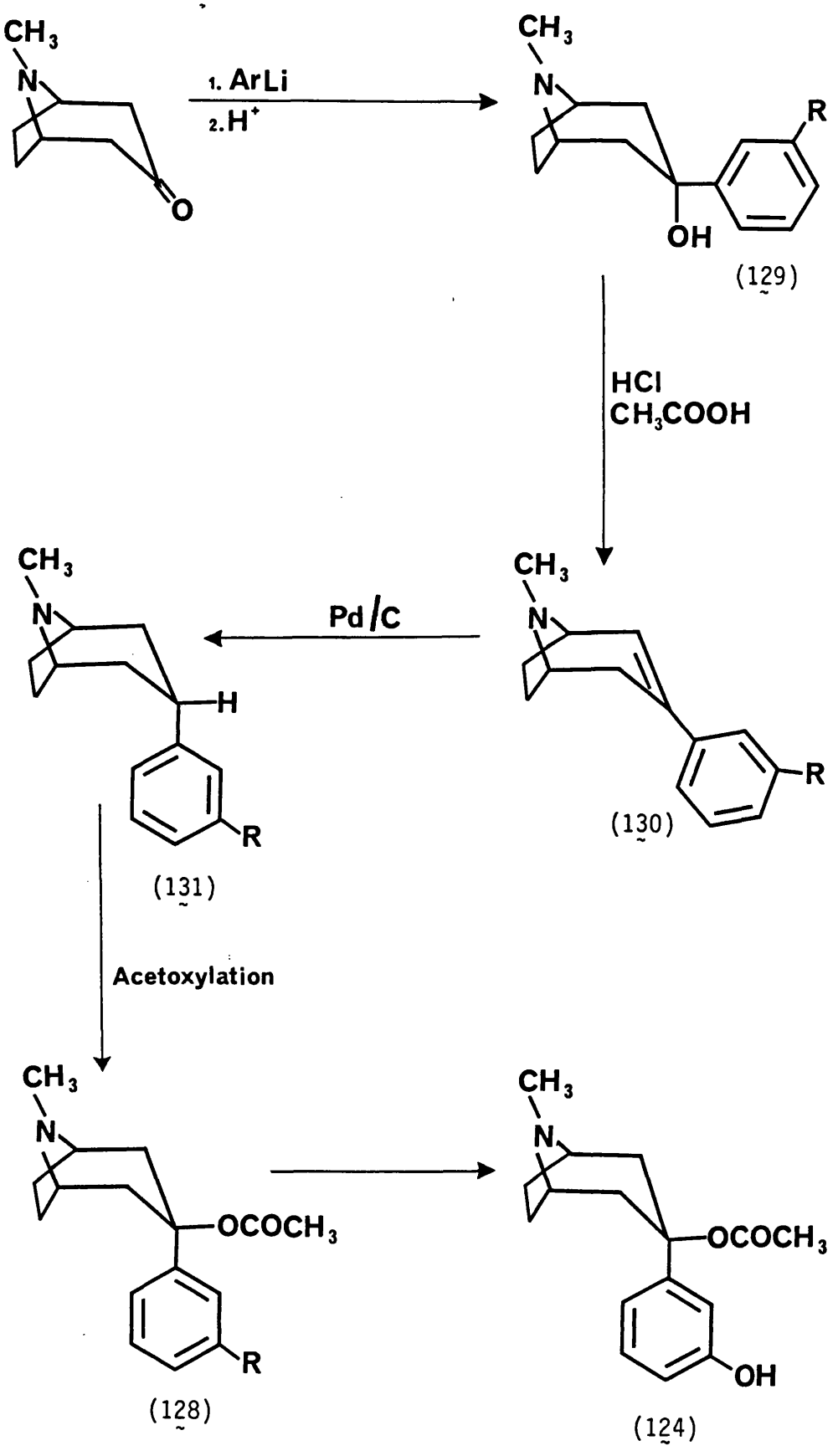
It was most probable that steric hindrance at the C-3 induced by the bulky aryl moiety was an important factor in the resistance of the alcohol to undergo esterification.

After numerous attempts to effect this esterification, it was decided to abandon this synthetic approach (as expressed in Scheme 20). Attention was then directed to the synthesis of 3β-acetyloxy-3α-(3-hydroxyphenyl)tropane (124).

2.2.3.2 The attempted synthesis of 3β-acetyloxy-3α-(3-hydroxyphenyl)tropane (124)

The proposed route of synthesis of 3β-acetyloxy-3α-(3-hydroxyphenyl)tropane is outlined in Scheme 21 (R=OMe).

It was anticipated that experimental difficulties would be encountered in the preparation of this tropane derivative (124). Consequently, the viability of this synthetic procedure was investigated by the synthesis of the 3α-phenyl analogue (128; R=H; Scheme 21). During the course of this preliminary work,


CH3
N
1. ArLi
2. H+
O
R
OH
(129)
HCl
CH3COOH
Pd/C
H
(131)
(130)
Acetoxylation
OCOCH3
(128)
(124)

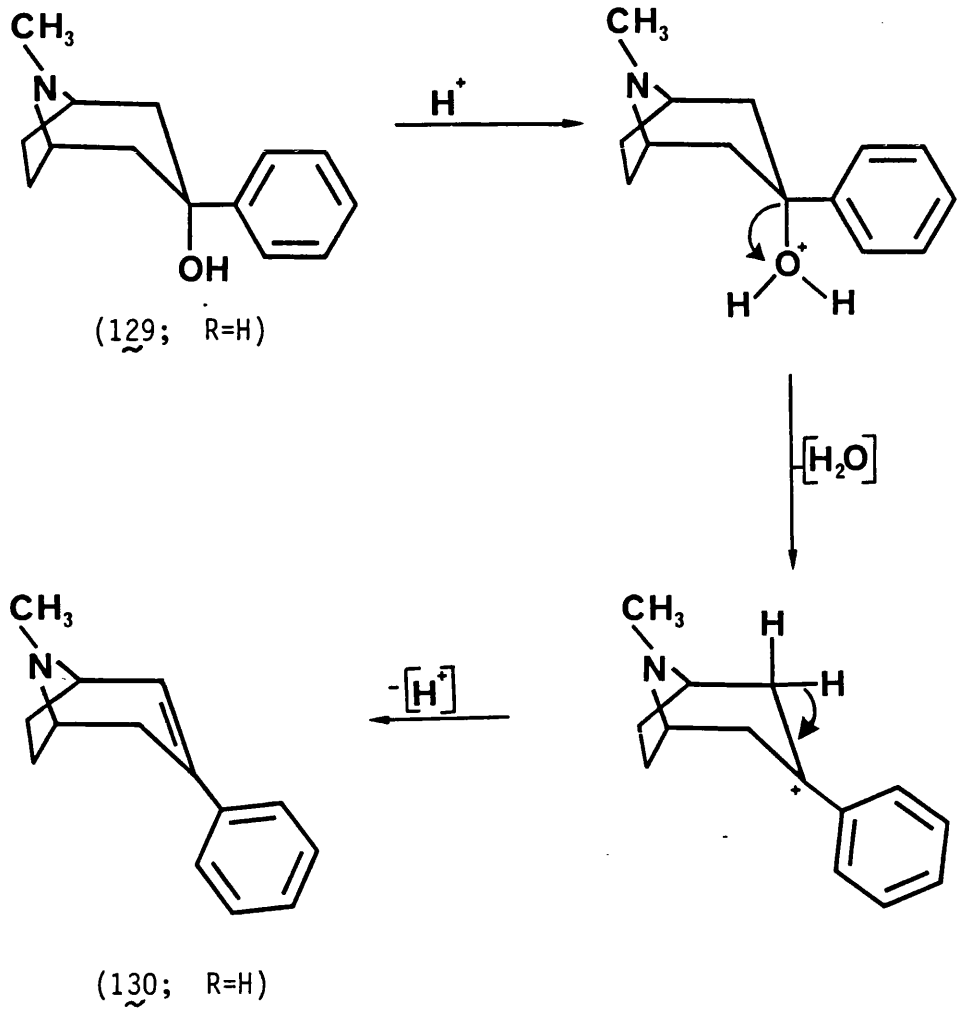
Scheme 21

stereochemical features associated with the tropane derivatives produced were investigated by ^{1}H-n.m.r. spectroscopy.

The attempted synthesis of 3β-acetyloxy-3α-phenyltropane (128; R=H)

As a starting point for this synthetic procedure, the tropanol (129; R=H) was produced by reaction of phenyl-lithium with tropan-3-one[121]. ^{1}H-n.m.r., ^{13}C-n.m.r. and IR spectra of this alcohol were consistent with its assigned structure. The stereochemical features of this alcohol have been established by ^{1}H-n.m.r. studies[122]. It exists in a preferred chair conformation (1(5)-H at δ3.23 with $W_{\frac{1}{2}}$=10Hz), with the hydroxy group axially orientated.

Acid catalysed dehydration of this alcohol was accomplished using concentrated HCl and glacial acetic acid[156], and furnished 3-phenyltrop-2-ene (130; R=H). This dehydration is considered to proceed via a two step E_1 mechanism as outlined in Scheme 22.



(129; R=H)

(130; R=H)

Scheme 22

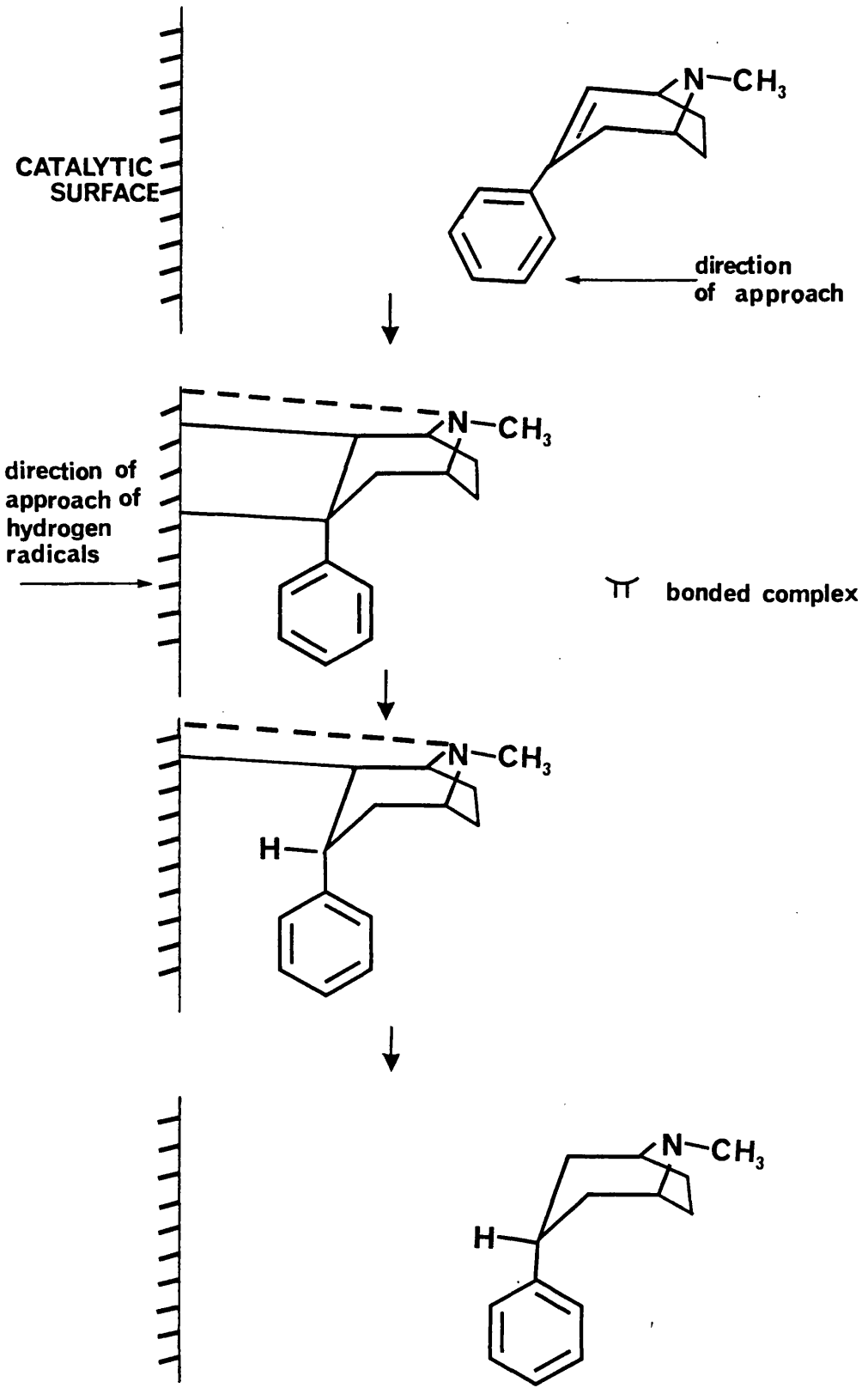
Confirmation of this olefinic product was provided by the detection of additional resonances in the 105-120 ppm region of the ^{13}C-n.m.r. spectrum, and the presence of an olefinic doublet at δ6.3 in the ^{1}H-n.m.r. spectrum.

Catalytic hydrogenation of 3-phenyltrop-2-ene yielded, exclusively, 3α-phenyltropane (131; R=H) as judged by ^{1}H- and ^{13}C-n.m.r. data.

The mechanism of catalytic hydrogenation is complex and still controversial. The generally accepted current theory suggests the adsorption of the substrate to the metallic catalyst surface forming a chemisorption complex[157-159]. Willstätter[160] and Ingold[161] envisaged that electrons are being transferred from the surface of the chemisorption complex to the substrate.

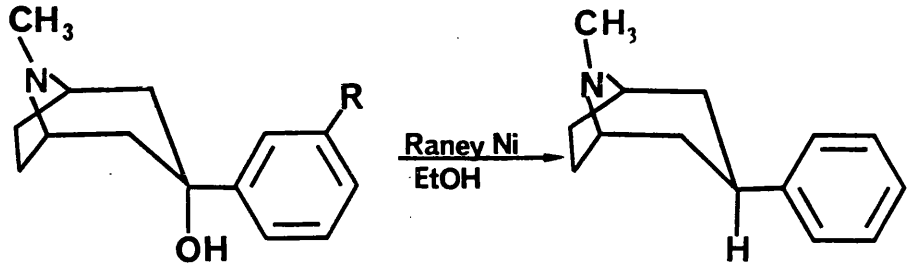
Stereochemically, the course of catalytic hydrogenation is complex. Evidence suggests that the adsorbed hydrogen is π bonded to the catalytic site[162], with the hydrogen radicals approaching from the less hindered side of the unsaturated substrate, yielding predominately cis-addition products[159] (see Scheme 23).

The hydrogenation of 3-phenyltrop-2-ene in this work was effected under hydrogen pressure of 60 p.s.i., catalysed by palladium charcoal. The ^{1}H-n.m.r. spectrum of the reduced product indicated the disappearance of the olefinic doublet. The configuration of the 3-phenyl group of the reduced product (131; R=H) is established as α- by ^{1}H-n.m.r. studies of the tertiary base. However, for comparative reasons it was desirable to analyse the spectral features of the epimeric congerer of (131; R=H); that is, 3β-phenyltropane (132)[163].


CATALYTIC SURFACE
N–CH3
direction of approach
direction of approach of hydrogen radicals
N–CH3
bonded complex
N–CH3
H
N–CH3
H

Scheme 23

The synthesis of (132) was achieved by the catalytic hydrogenolysis of the alcohol (129; R=H) using Raney-Nickel in ethanol (Scheme 24).



(129 R=H) (132)

Scheme 24

T.l.c. analysis of the reaction mixture revealed it to be a mixture of starting alcohol (129; R=H) and the desired tropane (132). Separation of these two tropane derivatives was achieved by distillation, although the yield of (132) was poor.

Catalytic hydrogenolysis of hydroxyl groups over Raney-Nickel is considered to be stereospecific[164,165], and the reaction proceeds with the retention of configuration. The poor yield of this hydrogenolysis can be attributed to the steric hindrance of the axially orientated hydroxyl group.

Spectral evidence for the preferred conformation and configuration of these two tropane derivatives is now presented (see Table 18, Nos. 4 and 5). Analysis of the 1(5)-H signal in the ^{1}H-n.m.r. spectrum suggests that both tropanes exist in a preferred chair conformation ($W_{\frac{1}{2}}$=9-10Hz). The tropane derivative (131; R=H) displayed two well resolved 6(7)-methylene resonances in the ^{1}H-n.m.r. spectrum (Δ=0.16 ppm). This separation can be attributed to

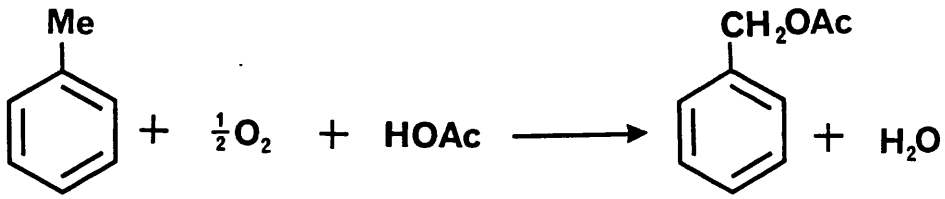
the shielding influence of the endo protons by an axial aromatic system[127]. However, the 6(7)-methylene resonance of the derivative (132) overlapped, evidence suggesting similar environments of the exo and endo protons, which is in accord with the assigned configuration.

Examination of the resonance signal for the C-3-H in the two epimeric tropanes (131; R=H) and (132) provided further evidence in support of the assigned configuration. In 3α-phenyltropane (131; R=H), with the C-3-H equatorial, the resonance signal at δ3.44 ppm appeared as a broad triplet (^{3}J=7-8Hz), as a result of two large and two small vicinal couplings. In 3β-phenyltropane (132), with an axial C-3-H, the resonance appeared as a seven line signal (centred at δ2.83) in accord with all vicinal couplings being large. Application of the Karplus relation[114] to these two epimers confirms these findings.

Having established the stereochemical features of 3α-phenyltropane, the final step in this reaction sequence involved the conversion of (131; R=H) to 3β-acetyloxy-3α-phenyltropane (128; R=H) by acetoxylation.

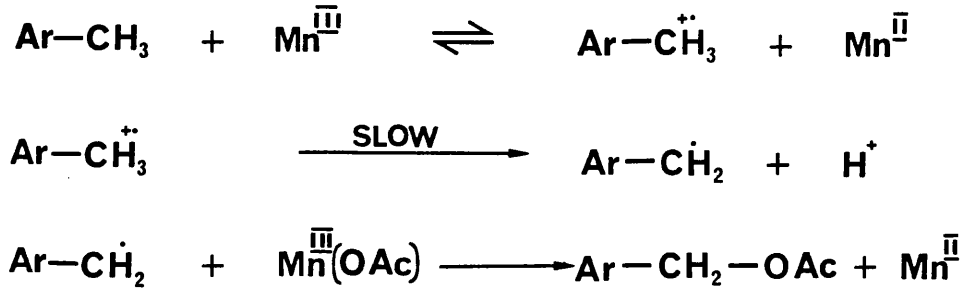
Acetoxylation is a procedure that has been used for the introduction of an acetoxy group into a hydrocarbon substrate and is applied synthetically as an indirect way of introducing an hydroxy substituent. Typical reagents utilized in this reaction are the transition metal salts (in acetic or trifluoroacetic acid) such as cobalt acetate ($Co(Ac)_3$)[166], chromyl acetate

($Cr_2O_7(OAc)_2$)[167], palladium acetate ($Pd(OAc)_2$)[168] and stannous acetate[169]. As an example to illustrate this type of reaction, it has been reported that benzyl esters are produced catalytically at moderate temperatures from methylbenzenes in a liquid phase process employing a homogenous palladium-stannous acetate catalyst and air[170] (Scheme 25).



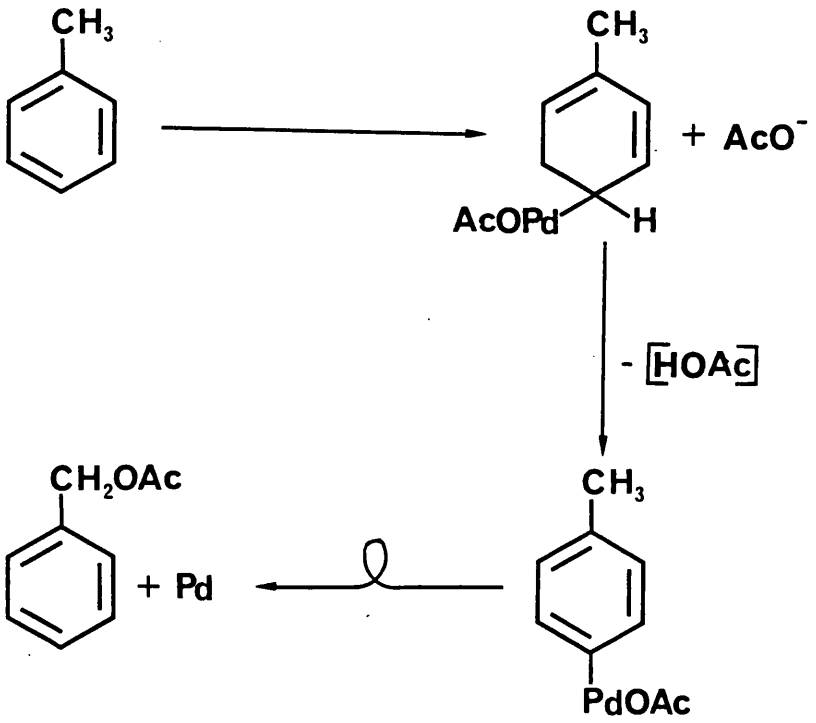
Scheme 25

The mechanism of such a palladium catalysed oxidation is not fully understood. Co(III) and Mn(III) oxidative substitution of arenes



Scheme 26

is considered to proceed via the formation of a radical-cation[171] (Scheme 26). However, Pd(II) is not a potent oxidant, and an alternative mechanistic explanation involves electrophilic aromatic substitution followed by rearrangement (Scheme 27)[172]. It is difficult to visualise a simple mechanism for the proposed rearrangement of a σ-aryl to σ-benzyl species[173] and, therefore, more studies are clearly needed before any definitive conclusions can be drawn about the mechanism of Pd(II) oxidation of arenes.



Scheme 27

In the present work, numerous attempts to effect this acetoxylation failed (using Pd(II)-stannous acetate), and returned starting material only. The attempted synthesis of the phenolic analogue (124) was therefore not undertaken.

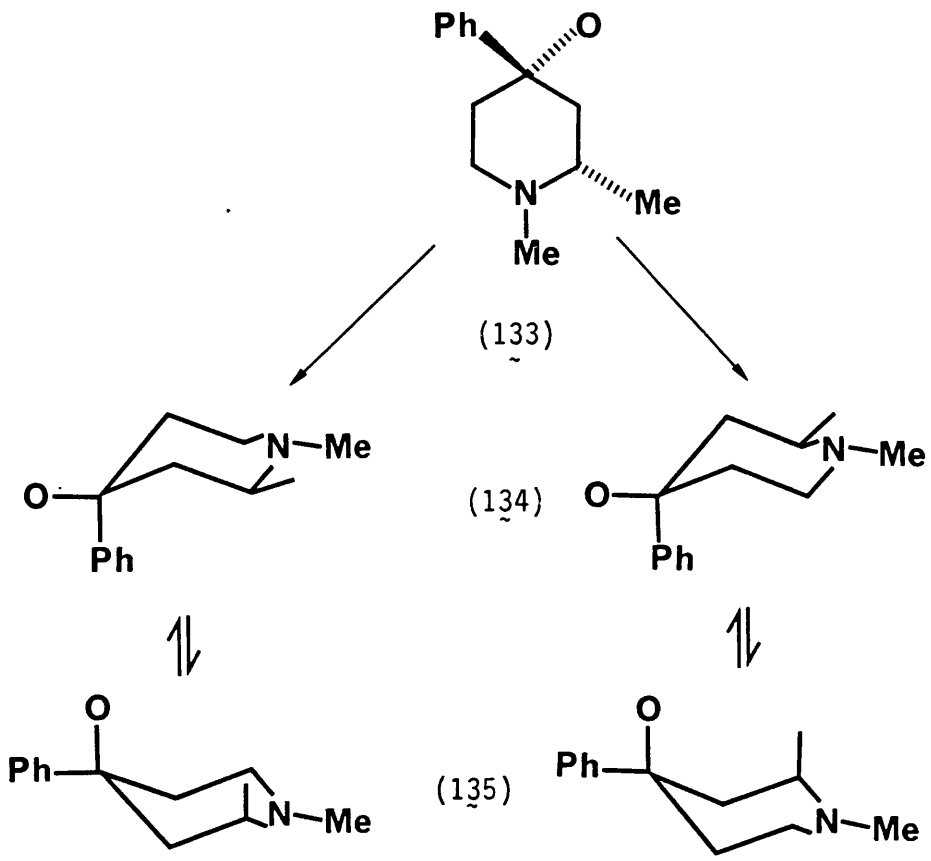
The termination of this work was justified so as to concentrate on the phenolic piperidine analogues (see section 2.3).

2.3 The Piperidines

2.3.1 Introduction

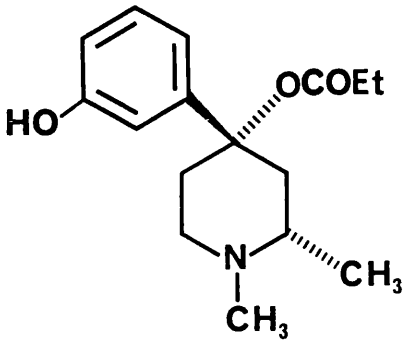
In 1972, Casy and McErlane[75] elucidated the relative configuration and conformation of α- and β-1,2-dimethyl-4-phenylpiperidin-4-ol by chemical means and ^{1}H-n.m.r. spectroscopy (see section 1.4.2.4.B). Furthermore, Portoghese and co-workers[91] succeeded in resolving the β-isomer into its two optical forms and determined the absolute configuration and analgesic potency of each enantiomer (see section 1.4.2.4.C). As part of this present work, the stereochemical assignments of α- and β- 1,2-dimethyl-4-phenylpiperidin-4-ol are substantiated by a 270MHz ^{1}H-n.m.r. study, and the availability of the α-isomer prompted the resolution of this diastereoisomer.

An assessment of the expected potency ratio of the two optical forms of the α-2-methyl analogue (133) can be made by application of the principles outlined in section 1.4.2.4.C. This 4-phenylpiperidine derivative exists in an axial 4-phenyl chair conformation with an equatorial 2-methyl substituent (see 134). However, for this analysis it is necessary to consider this derivative in the equatorial 4-phenyl chair conformation (see 135).

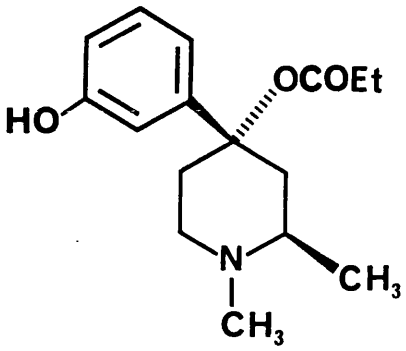


In this equatorial 4-phenyl chair conformation, the 2-methyl substituent has an axial orientation, and as it is adjacent to the nitrogen atom both antipodes possess favourably placed substituents. As this is the case, the potency ratio of the two antipodal forms would be expected to be unity.

Attention was also given to the synthesis and stereochemical characterization of the two phenolic derivatives (136) and (137). Initial attempts to effect this synthesis utilized the procedure



(136)



(137)

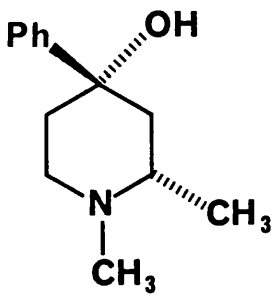
described by Portoghese et al.[56] with phenolic-OH protection by methyl. Such an approach proved unsatisfactory, and therefore the synthetic procedure described by Casy and Ogungbamila[57] was utilized which successfully gave rise to the two desired derivatives. The stereochemical features of these two diastereoisomers was determined by ^{1}H-n.m.r. spectroscopy.

In a six-membered ring chair system the order of magnitude of diaxial (Jaa), axial-equatorial (Jae) and diequatorial (Jee) coupling constants in the ^{1}H-n.m.r. spectrum can be predicted from the angular relationships of the protons by application of the Karplus relationship[114] (see page 76). ^{3}J values are therefore largest when the vicinal protons are trans-coplanar ($\phi = 180^0$), slightly less when they are cis-coplanar ($\phi = 0^0$), and almost zero when the protons are at right angles. Thus, Jaa values generally fall within 8-14Hz, while Jae and Jee values fall within 1-6Hz[115].

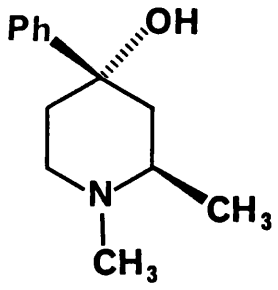
2.3.2 Synthesis and stereochemistry of the isomeric 1,2-dimethyl-4-phenylpiperidin-4-ols

2.3.2.1. Synthesis

1,2-Dimethyl-4-piperidone (138; Scheme 28), the key intermediate in the synthesis of the diastereoisomeric alcohols (139) and (140), was prepared as outlined in Scheme 28.



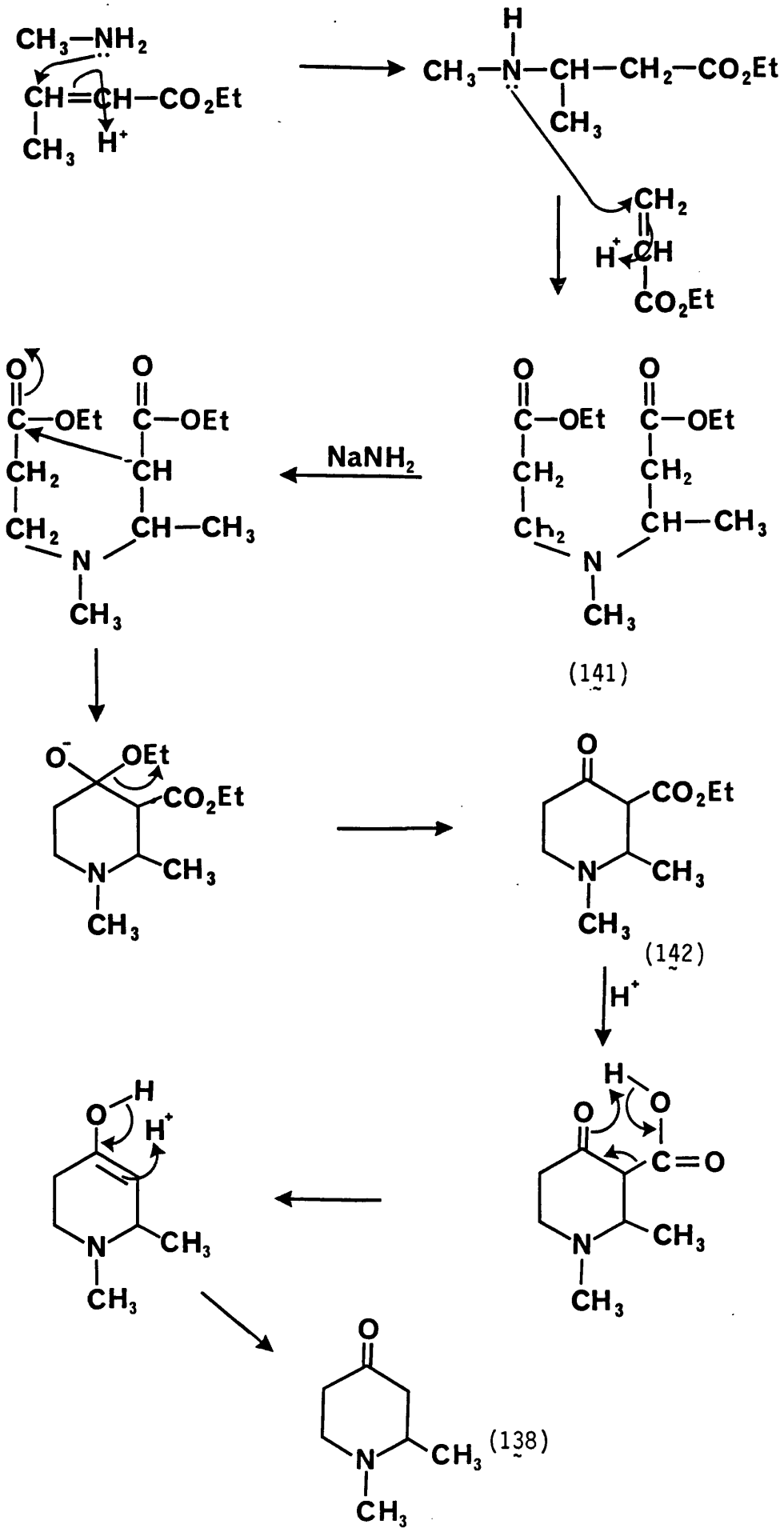
(139)



(140)

This synthesis involved the stepwise Michael condensation[148-150] of ethyl crotonate and then ethyl acrylate to methylamine yielding the diester (141). This diester in the presence of $NaNH_2$ underwent Dieckmann cyclization[174] to give the 3-carboethoxy-4-piperidone (142). Hydrolysis followed by decarboxylation of (142) yielded the required 1,2-dimethyl-4-piperidone (138).

The reaction of phenyl-lithium with the piperidone (138) gave a mixture composed of almost equal amounts of the two isomers (139) and (140) as judged by the 1- and 2-methyl ^{1}H-n.m.r. signals. Separation of the two isomers was achieved by fractional crystallisation of the free base. The first crop was shown to be


CH3—NH2
CH=CH—CO2Et
CH3
H+
CH3—N—CH—CH2—CO2Et
H
CH3
CH2
H+CH
CO2Et
NaNH2
(141)
(142)
H+
(138)

Scheme 28

the β-isomer (140), while the second crop was the α-isomer (139). It was fortuitous that the separation proceeded smoothly, as procedures recorded in the literature demanded the use of column chromatography[75].

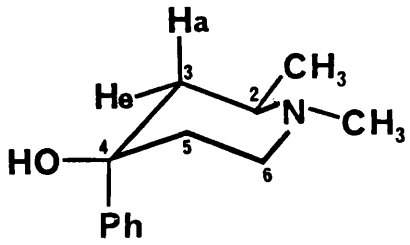
The availability of these two isomeric alcohols prompted a ^{1}H-n.m.r. study of their stereochemical characteristics, and the resolution of the α-alcohol (139) was also undertaken.

2.3.2.2 Stereochemical studies of the isomeric 1,2-dimethyl-4-phenylpiperidin-4-ols

The stereochemistry of the isomeric alcohols (139) and (140) has been the subject of previous investigations and is well established[66,75]. The present study, due to the availability of 270MHz ^{1}H-n.m.r. spectroscopy, confirms the stereochemical assignments already made.

A. α-1,2-Dimethyl-4-phenylpiperidin-4-ol

Previous studies of the chemical and spectral features of the alcohol (139) supported the configuration c-2-Me, r-4-OH[66,75]. Evidence to suggest that this derivative exists as an axial-4-phenyl chair (143) is provided by analysis of the ^{1}H-n.m.r. coupling constants (base in $CDCl_3$; Table 21, No. 1).



(143)

Proof that the C-2-methyl group has an equatorial orientation and hence the 4-phenyl group is axially orientated is provided by examination of the C-2-H resonance coupling pattern. The C-2-H is coupled to two C-3-H protons (one axial Ha and one equatorial He) and the C-2-methyl protons, giving rise to a multiple signal. Examination of the spectrum revealed a twelve line multiplet (centred at δ2.4 ppm). Decoupling experiments were therefore necessary to resolve the C-2-H resonance in order to determine the vicinal ^{3}J values. Spin decoupling of the C-2-methyl doublet at δ1.1 ppm resolved the C-2-H resonance into a doublet of doublets (see Fig.10) with ^{3}J=11.2 and 3.1Hz. These two ^{3}J values are typically those of an axial-axial and an axial-equatorial coupled proton respectively. Therefore, the C-2-H has an axial orientation and hence the C-2-methyl must be equatorial. In order to further substantiate this finding, analysis of the ^{1}H-n.m.r. spectrum to extract the coupling data of the two C-3-H was necessary. The resonance signals at δ2.8 (^{2}J=11.8Hz, ^{3}J=4.34Hz (Jee) and 2.48Hz (Jae)) and δ2.62 (^{2}J=11.8Hz, ^{3}J=11.8Hz (Jaa) and 2.48Hz (Jae)) were assigned to the equatorial and axial C-6-H respectively. The

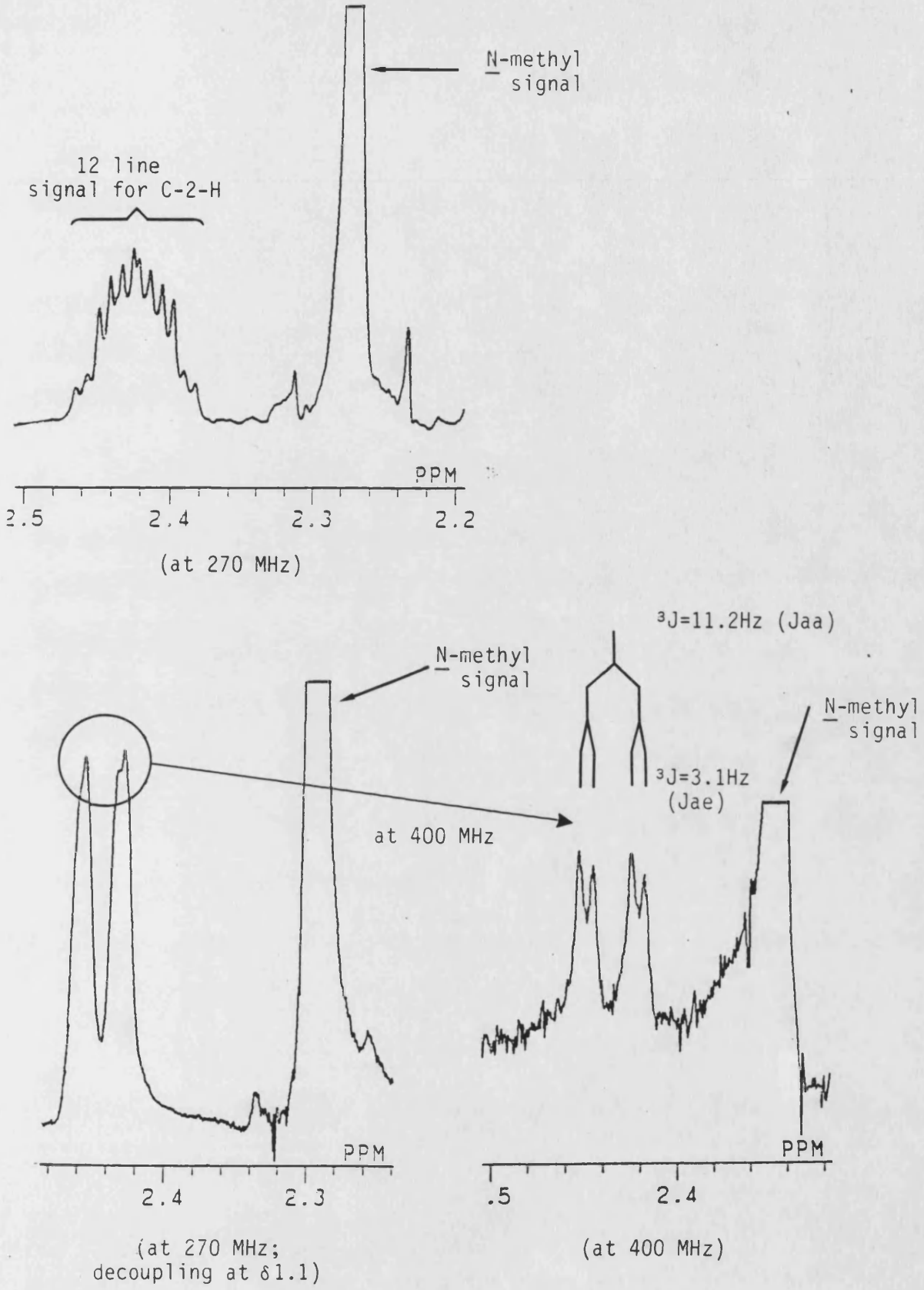
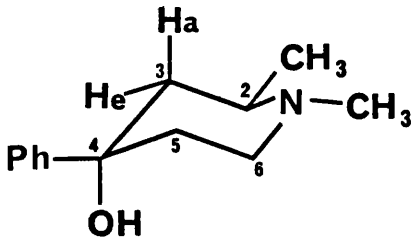


Figure 10 Partial ^{1}H-n.m.r. spectrum and Spin Decoupled spectra of α-1,2-dimethyl-4-phenylpiperidin-4-ol (as base in $CDCl_3$).

resonance signal at δ2.20 (^{2}J=13.6Hz, ^{3}J=13.6Hz (Jaa) and 5.00Hz (Jae)) was assigned as the axial C-5-H (decoupling of axial C-2-H did not affect this signal). Unfortunately, the three other ring protons, namely, the equatorial C-5-H, equatorial C-3-H and the axial C-3-H were part of a complex multiplet centred at δ1.75 ppm and hence no useful stereochemical information could be gained from this signal.

B. β-1,2-Dimethyl-4-phenylpiperidin-4-ol

The configuration of the β-alcohol (140) has been established as t-2-Me, r-4-OH based on chemical and spectral evidence[66,75]. The ^{1}H-n.m.r. (270MHz) spectrum provided evidence in support of an equatorial C-2-methyl and hence an equatorial 4-phenyl as in the conformation (144; base in $CDCl_3$; Table 21, No.2).



(144)

The C-2-H signal was not resolved and was part of a complex multiplet (δ2.1 to δ2.4 ppm). However, one of the C-3-methylene protons was resolved and the magnitude of the ^{3}J value shows axial-axial coupling (^{3}J=10.5Hz) to be involved. This resonance

therefore can be attributed to the axial C-3-H, coupling with an axial C-2-H. Hence, the 2-methyl group must be equatorially orientated.

With the exception of the equatorial C-6-H (δ2.8 ppm, ^{2}J=11.75Hz, ^{3}J=2.6Hz (Jea, Jee)), all other ring protons were not resolved and so no further information on the conformation could be deduced from this data.

The stereochemical features of the two alcohols (139) and (140) as described above confirm the preferred conformation of each diastereoisomer. The principles outlined will be utilized in analysis of the stereochemistry of the phenolic analogues (section 2.3.4).

2.3.3 Resolution of (±)-α-1,2-dimethyl-4-phenylpiperidin-4-ol

As part of the continued interest in the analgesic activity of the two optical forms of the diastereoisomeric pethidine reversed esters, resolution of (±)-α-1,2-dimethyl-4-phenylpiperidin-4-ol (139) was undertaken to give (+)- and (-)-α-1,2-dimethyl-4-phenylpiperidin-4-ol. Esterification of each enantiomer with acetyl chloride afforded the corresponding acetate esters as the hydrochloride salts (Scheme 29).

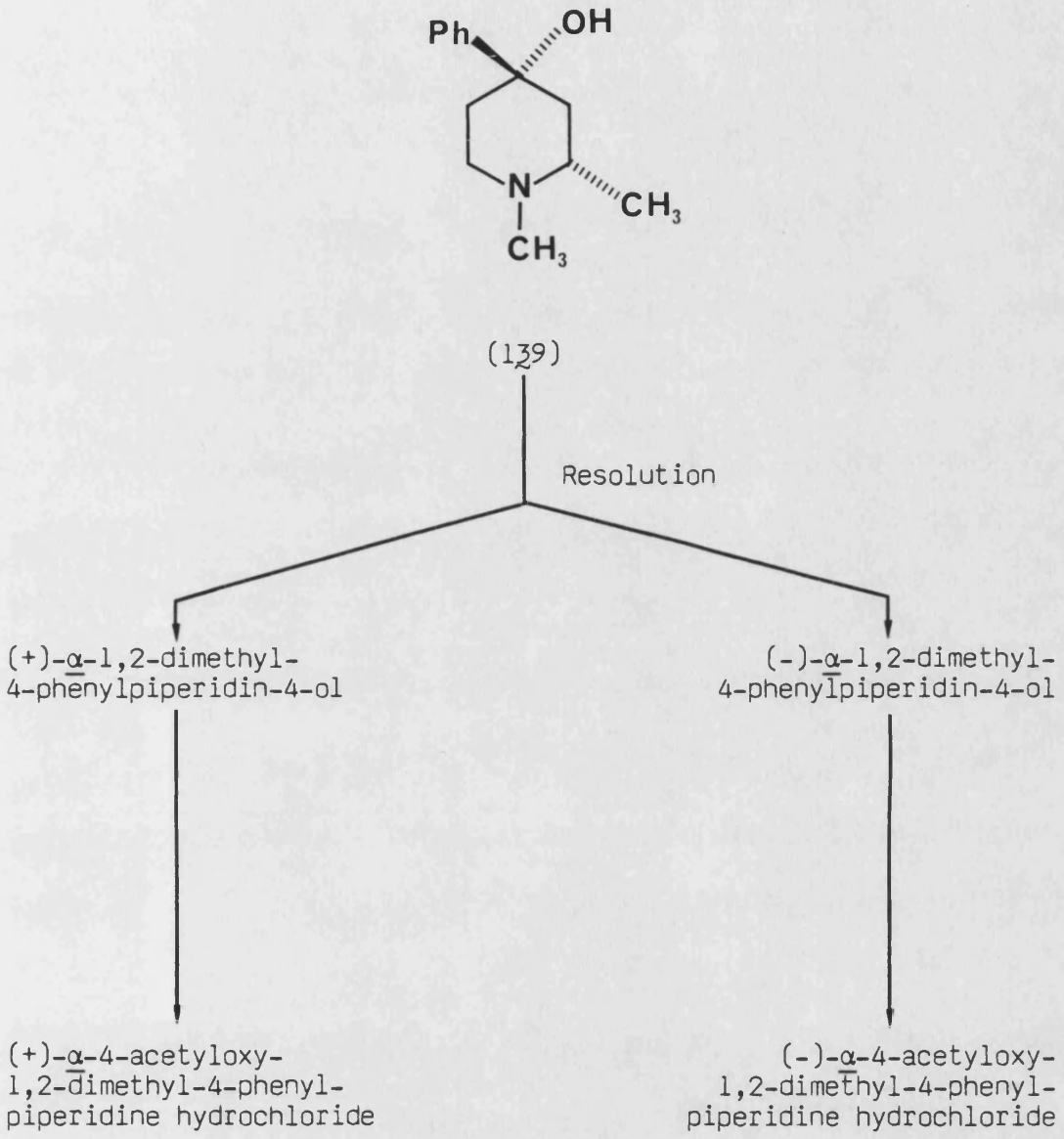
The term 'resolution' or 'optical resolution' is generally defined as a procedure through which both optical isomers (enantiomers) are separated in the purified state from a racemic mixture. Through years of investigation, Pasteur and his colleagues[175] developed various methods which are the main means of resolution today. These methods include:

(a) resolution by entrainment[176],

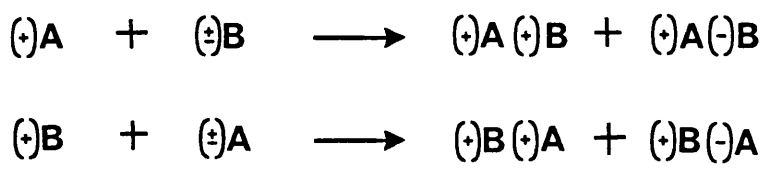
(b) resolution *via* diastereoisomeric salt formation[175],

(c) biochemical resolution[177].

The resolution of (±)-α-1,2-dimethyl-4-phenylpiperidin-4-ol was achieved by diastereoisomeric salt formation. This procedure involves the interaction of racemic bases (B) with optically active acids (A) or racemic acids with optically active bases. Thus, enantiomers are transformed to diastereoisomeric salts which may then be separated by differential solubility (Scheme 30).


Ph
OH
N
CH3
CH3
(139)
Resolution
(+)-α-1,2-dimethyl-4-phenylpiperidin-4-ol
(-)-α-1,2-dimethyl-4-phenylpiperidin-4-ol
(+)-α-4-acetyloxy-1,2-dimethyl-4-phenyl-piperidine hydrochloride
(-)-α-4-acetyloxy-1,2-dimethyl-4-phenyl-piperidine hydrochloride

Scheme 29



Scheme 30

The diastereoisomeric salts cropped after fractional crystallisation can then be hydrolyzed with inorganic alkalis or acids to give the enantiomers. This procedure usually involves many recrystallisations, monitored by polarimetry.

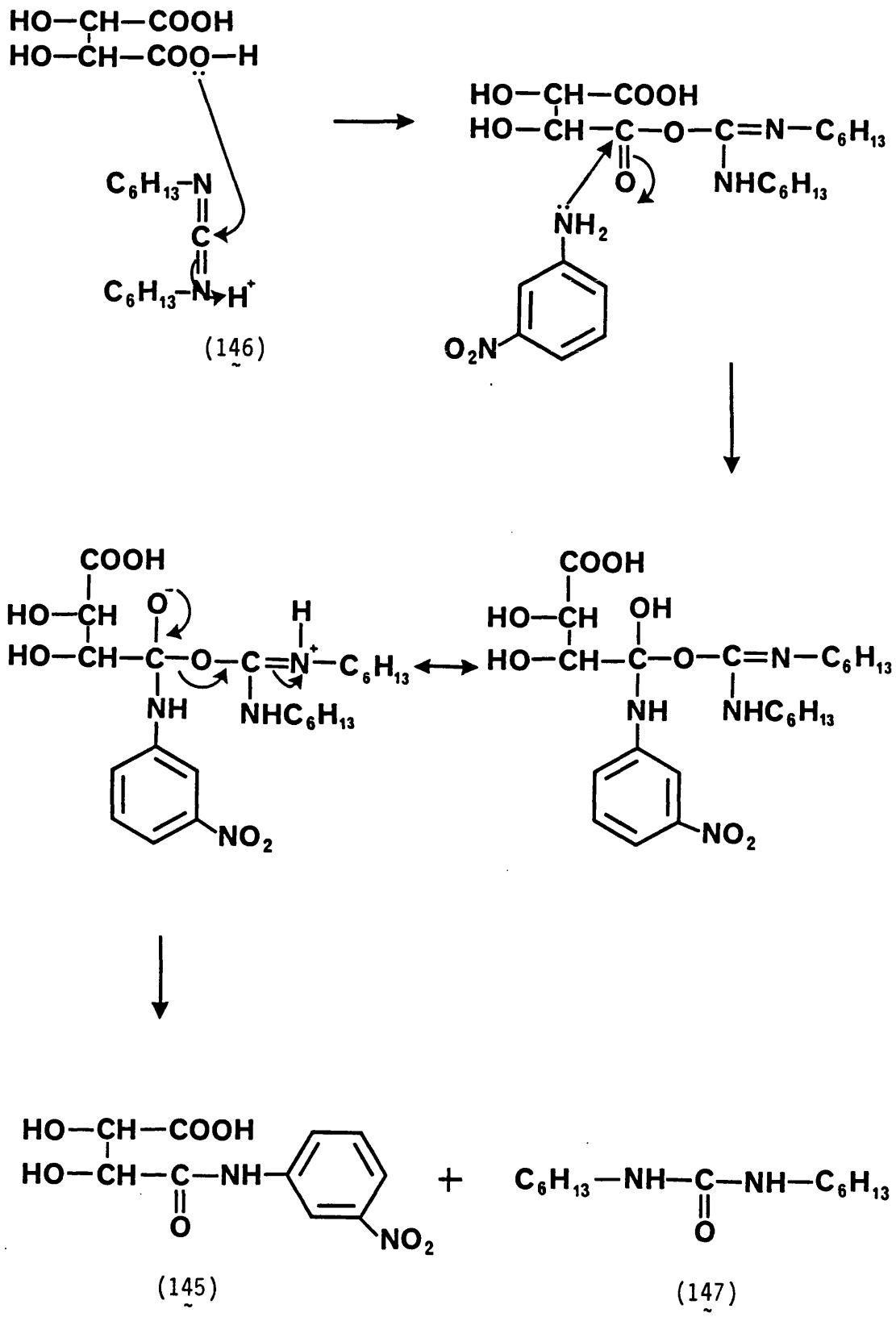
Common optically active acids used for the resolution of racemic bases include tartaric acid, mandelic acid, camphoric acid and camphor-10-sulphonic acid. Optically active bases such as morphine, ephedrine and menthylamine are used for resolving racemic acids. The conditions necessary to effect resolution cannot be generalised, although the choice of optically active resolving agent and the solvent are important considerations.

Optical resolution of (±)-α-1,2-dimethyl-4-phenylpiperidin-4-ol (139) was achieved through fractional crystallisation of the 3'-nitrotartranilate salts. (+)-3'-nitrotartranilic acid (145) was prepared by reacting (+)-tartaric acid with 3-nitroaniline in the presence of dicyclohexylcarbodiimide (146).

Dicyclohexylcarbodiimide (DCC) is an effective catalyst for the condensation of carboxylic acids with alcohols and amines[178]. Thus, an equimolar mixture of the carboxylic acid ((+)-tartaric acid), an amine (3-nitroaniline) and DCC result in the corresponding amide (145) and the highly insoluble N,N'-dicyclohexylurea (147; Scheme 31).

The nitrotartranilate of (+)-α-1,2-dimethyl-4-phenylpiperidin-4-ol has a specific rotation of -60.0° and the nitrotartranilate of its enantiomer has an specific rotation of +60.0°. Basification of the two salts generated (+)-α-1,2-dimethyl-4-phenylpiperidin-4-ol with a specific rotation +1.0° and (-)-α-1,2-dimethyl-4-phenylpiperidin-4-ol with a specific rotation -1.0°, (also see Experimental, page 219).

Esterification of the (+)- and (-)-α-1,2-dimethyl-4-phenylpiperidin-4-ol with acetyl chloride in toluene afforded, respectively, (+)-α-4-acetyloxy-1,2-dimethyl-4-phenylpiperidine and (-)-α-4-acetyloxy-1,2-dimethyl-4-phenylpiperidine as the hydrochloride salts.



(146)

(145)

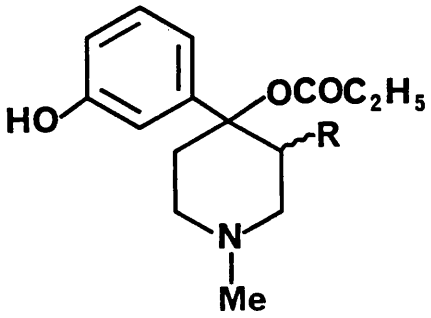
(147)

Scheme 31

2.3.4 The synthesis of α- and β- 1,2-dimethyl-4-(3-hydroxyphenyl)-4-propionyloxypiperidine

2.3.4.1 Unsuccessful synthesis

Initial attempts to secure the two phenolic esters (136) and (137) involved application of the synthetic procedure used in the synthesis of the 3-methyl (35) and 3-allyl (36) analogues of the reversed esters of pethidine, as described by Portoghese et al.[56].



α: c-3-R, r-4-OCOEt

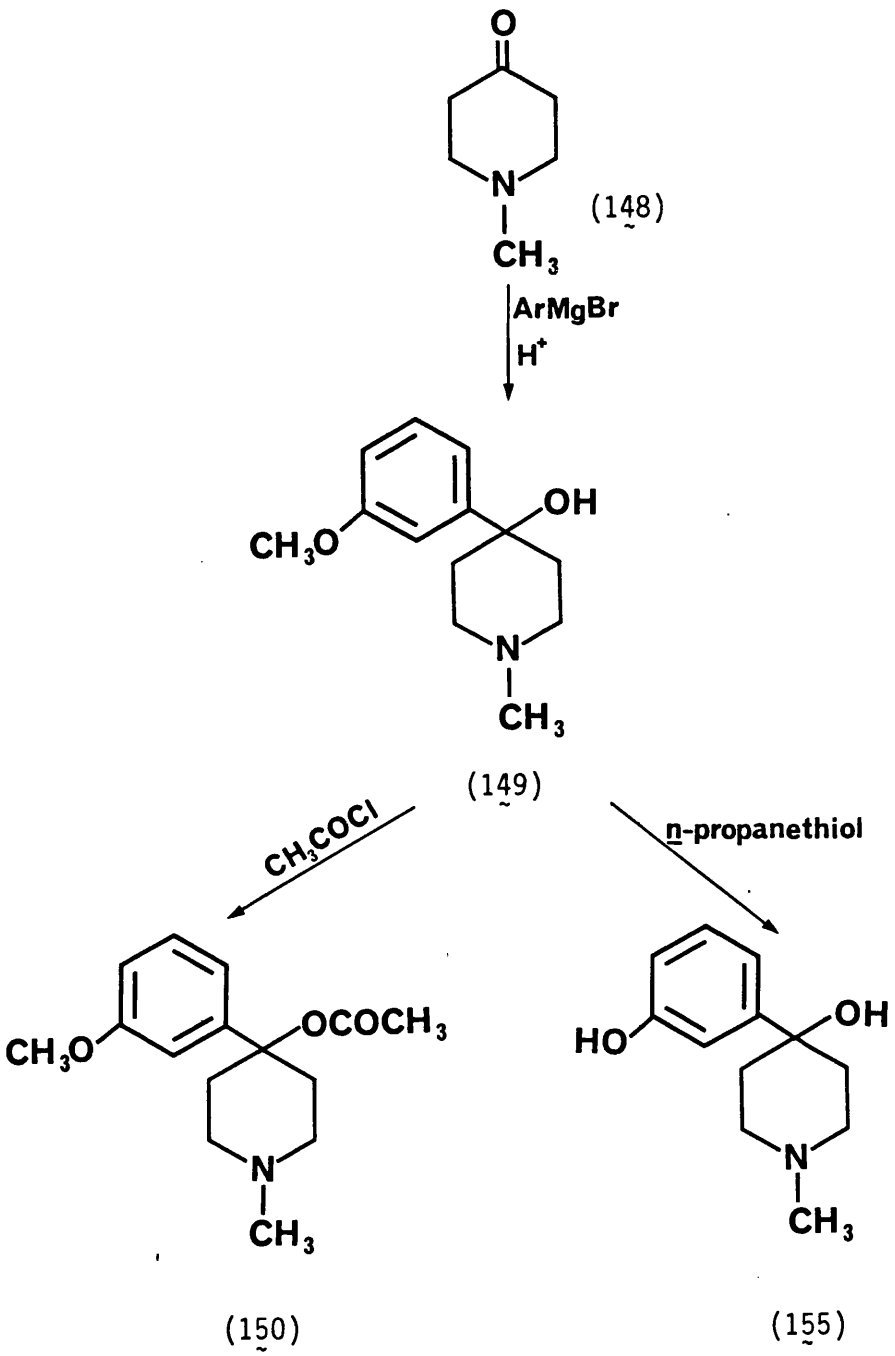
β: t-3-R, r-4-OCOEt

(35) R=Me

(36) R=$CH_2CH=CH_2$

A preliminary investigation into the suitability of this procedure was undertaken using 1-methyl-4-piperidone (148; Scheme 32).

Reaction of 1-methyl-4-piperidone (148) with the Grignard reagent derived from 3-bromoanisole and magnesium furnished the alcohol (149). Characterisation of this alcohol was achieved by ^{1}H-n.m.r., ^{13}C-n.m.r. and IR spectra, one notable feature being the absence of carbonyl absorption (a characteristic of starting ketone) in the ^{13}C-n.m.r. and IR.



(148)

(149)

(150)

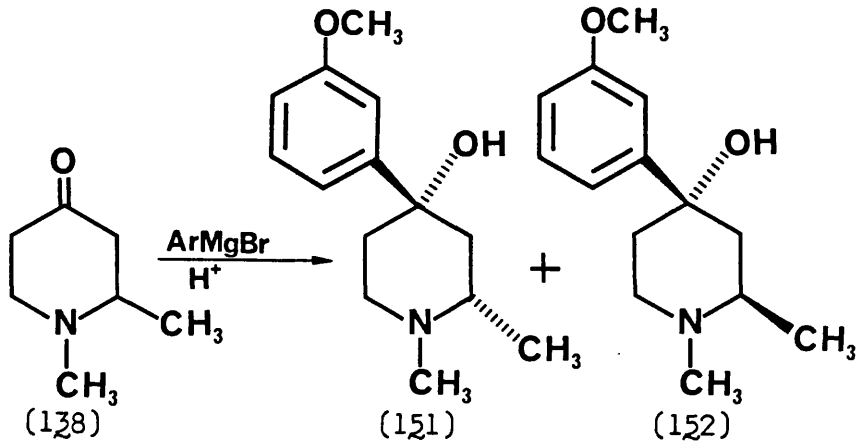
(155)

Scheme 32

Esterification of (149) with acetyl chloride afforded (150) as illustrated in Scheme 32. The IR spectrum of this compound displayed strong absorption at 1750 cm^{-1}, characteristic of ester carbonyl. Acetyloxy carbonyl was observed at 169.4 ppm in the ^{13}C-n.m.r. Another important feature confirming esterification was the downfield chemical shift (approximately 9-10 ppm) of the C-4 quaternary carbon in the ^{13}C-n.m.r. due to a stronger deshielding effect of OCO group over the OH group of the alcohol (C-4 in alcohol (149) at 69.97 ppm; C-4 in ester (150) at 79.70 ppm).

Following the success of this procedure using 1-methyl-4-piperidone, the attempted synthesis of the two isomeric alcohols (151) and (152) was undertaken.

Reaction of 1,2-dimethyl-4-piperidone (138) with the Grignard reagent derived from 3-bromoanisole yielded an oil which by t.l.c. analysis appeared as a mixture of two compounds (neither of which correspond to the starting ketone). The IR spectrum of this oil indicated disappearance of carbonyl absorption and the appearance of OH absorption (Scheme 33).

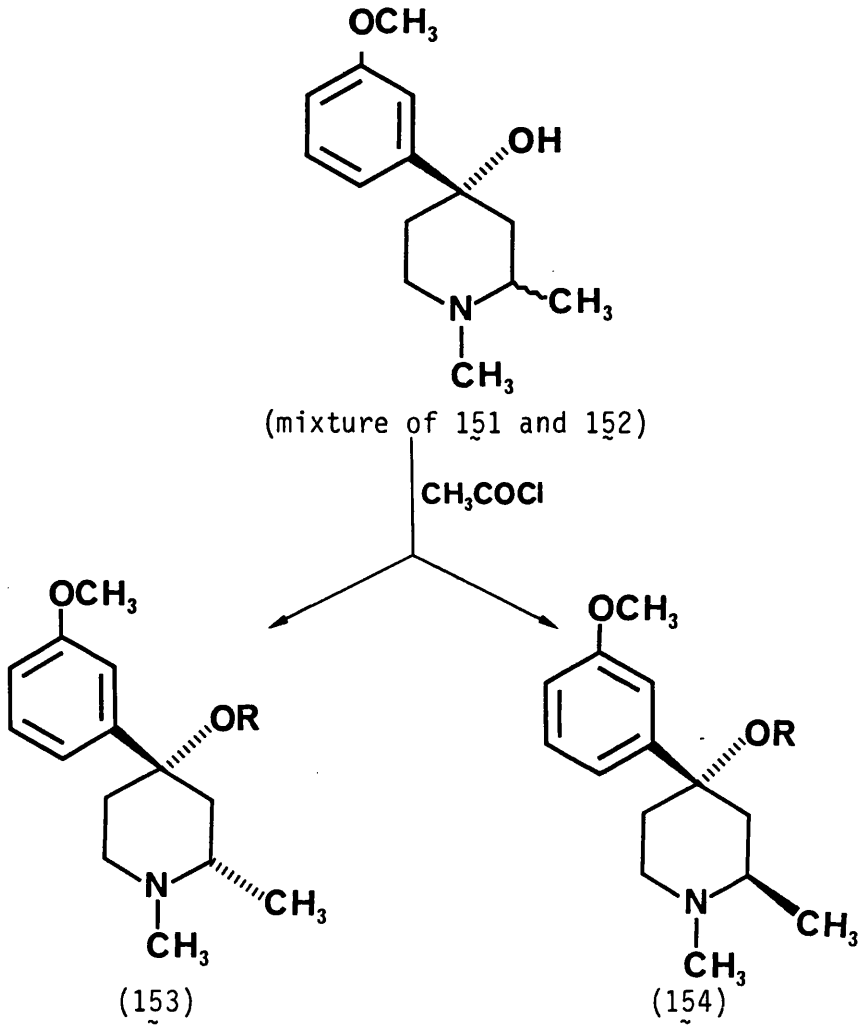


(138) (151) (152)

Scheme 33

The attempted separation of this isomeric mixture of alcohols proved unsuccessful - crystallization of the base or a variety of salts such as the hydrochloride, oxalate and maleate all failed.

Following the failure to effect separation of the two alcohols, the isomeric mixture was converted to the corresponding esters (153; $R=COCH_3$) and (154; $R=COCH_3$). The esterification was achieved by treatment of the isomeric mixture of alcohols with acetyl chloride (Scheme 34). The resultant oil displayed characteristic ester carbonyl at 1765 cm^{-1}. All attempts at the separation of these two isomeric esters also failed.



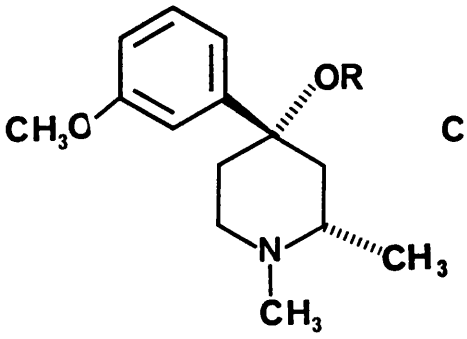
Scheme 34

As it proved impossible to separate either the isomeric alcohols or esters, O-demethylation of the isomeric alcohols to the corresponding phenols was undertaken. O-Demethylation of the alcohol (149) witn n-propanethiol[179,180] yielded the corresponding phenolic alcohol[56] (155; Scheme 32). The ^{13}C-n.m.r. spectrum of this alcohol showed absence of the O-CH_3 signal. The use of the propanethiolate anion as a means of O-demethylation arises because of the susceptibility of the piperidinol (149) to undergo dehydration under acidic conditions.

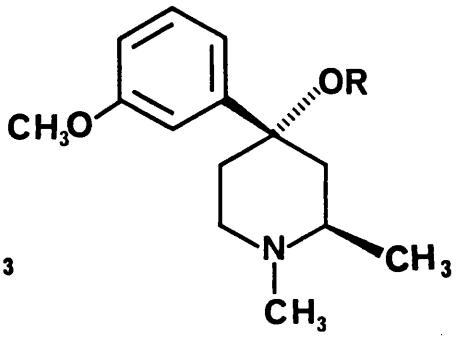
O-Demethylation of the isomeric alcohols (151) and (152) yielded an oil which darkened on standing and proved intractible. This attempted synthesis was therefore abandoned.

2.3.4.2 Successful synthesis

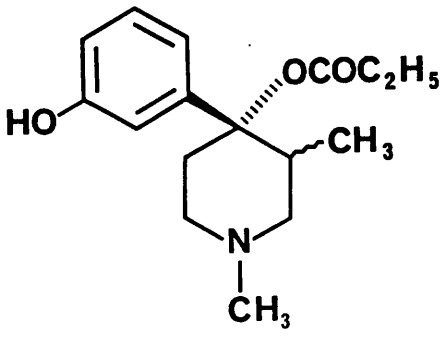
In view of the difficulties experienced in separating the two isomers (153; R=H or $COCH_3$) and (154; R=H or $COCH_3$), application of the synthetic procedure described by Casy and Ogungbamila[57] for the synthesis of the phenolic esters (35) and (156) was undertaken. This procedure utilized the Grignard reagent derived from 3-(2'-tetrahydropyranyloxy)bromobenzene (157; Scheme 35)[181].



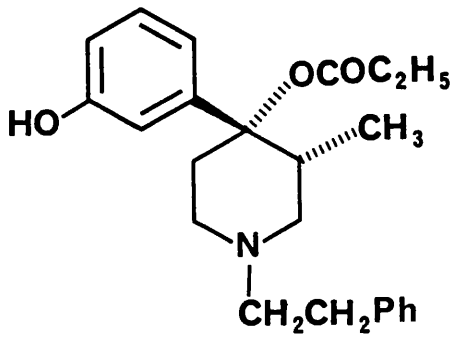
(153)



(154)



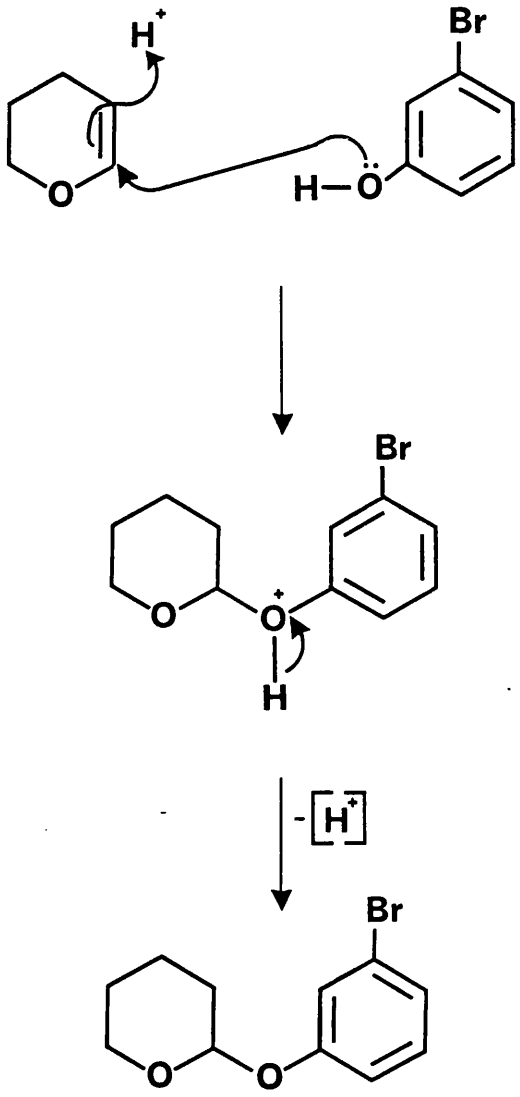
(35)



(156)

α: c-3-CH_3, r-4-OCOEt

β: t-3-CH_3, r-4-OCOEt

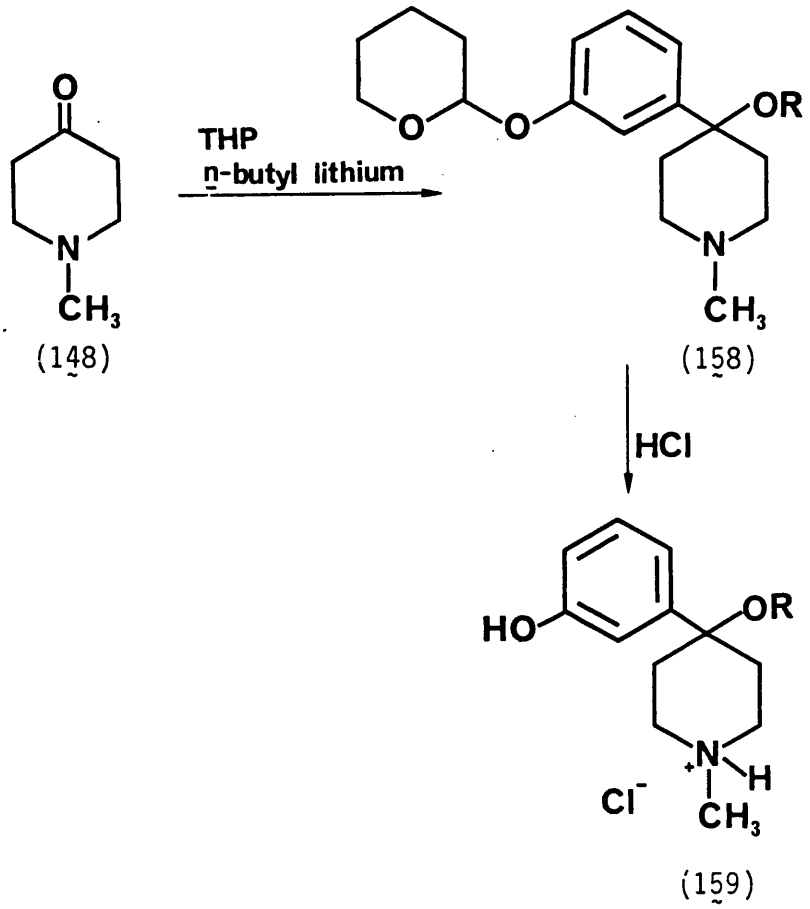


(157)

Scheme 35

3-(2'-Tetrahydropyranyloxy)bromobenzene (THP) was synthesised by reaction of 3-bromophenol and dihydropyran in the presence of a catalytic quantity of concentrated hydrochloric acid (Scheme 35).

Initial investigatory experiments of the suitability of this procedure (using 1-methyl-4-piperidone (148)) were undertaken (Scheme 36).



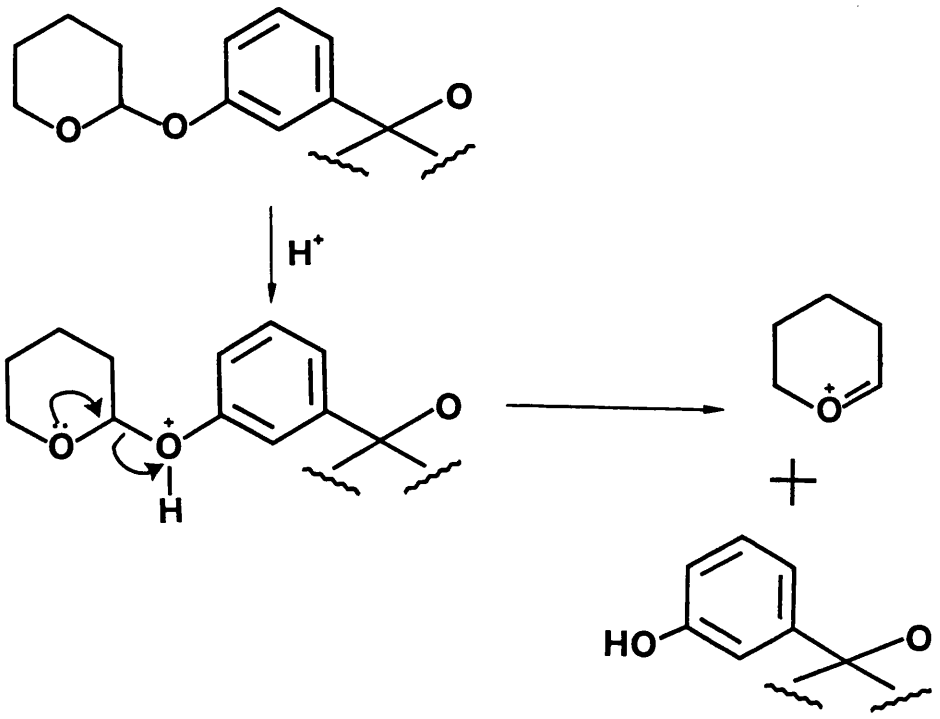
(148) (158) (159)

Scheme 36

The preparation of the Grignard reagent derived from THP and magnesium was unsuccessful. A variety of techniques were employed

to promote Grignard formation, all of which failed. These included the use of initiators such as iodine and 1,2-dibromoethane, and washing the magnesium with concentrated hydrochloric acid to remove surface oxides. However, reaction of THP with n-butyl lithium successfully generated the corresponding organometallic reagent.

Reaction of this organometallic reagent with 1-methyl-4-piperidone, followed by decomposition of the resultant complex with acetic anhydride, furnished the protected ester (158; $R=COCH_3$; Scheme 36), which on treatment with ethanolic hydrogen chloride gave the free phenol (159; $R=COCH_3$; Scheme 36) directly as the



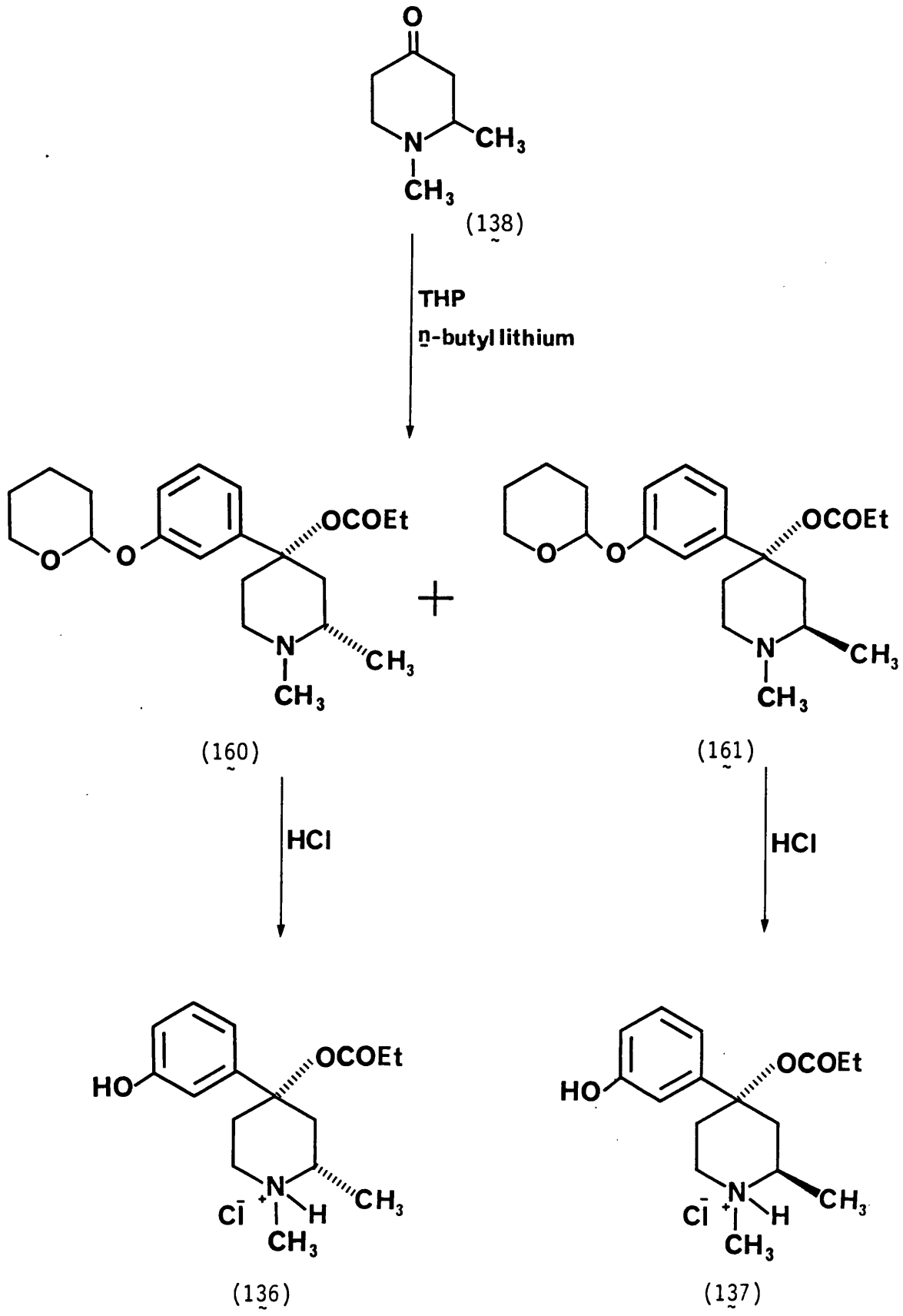
Scheme 37

hydrochloride salt. This treatment of the protected ester by hydrogen chloride yields the phenolic ester by virtue of the acid susceptibility of the acetal portion of the THP ether to undergo hydrolysis (Scheme 37).

The synthesis of the free phenol[56,57] (159; R=COC_2H_5) was achieved by a similar procedure using propionic anhydride for the decomposition of the complex derived from the reaction of 1-methyl-4-piperidone and the organometallic reagent derived from THP and n-butyl lithium.

Characterisation of these two phenolic esters was achieved by ^1H- and ^{13}C-n.m.r. spectroscopy. Each spectrum displayed the appropriate aromatic and ester signals in accord with the assigned structures.

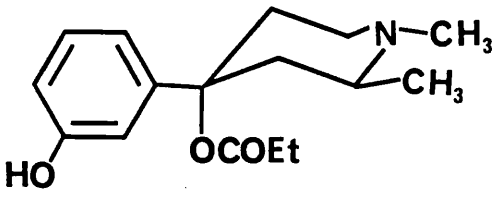
Having secured a synthetic procedure for the synthesis of the free phenols (159; R=$COCH_3$ or COC_2H_5), the synthesis of the phenolic derivatives (136) and (137) was undertaken. Treatment of 1,2-dimethyl-4-piperidone (138) with the organometallic reagent derived from THP and n-butyl lithium yielded an isomeric mixture of (160) and (161) as judged by t.l.c. analysis (Scheme 38). Separation of the two protected esters was achieved by utilizing the differential solubility of their propionate salts. The β-isomer was obtained as the propionate salt from the reaction medium by the addition of ether. The α-isomer was not deposited by the addition of ether, and was obtained as the base from the mother liquors.


O
N
CH3
CH3
(138)
THP
n-butyl lithium
OCOEt
O
O
N
CH3
CH3
(160)
OCOEt
O
O
N
CH3
CH3
(161)
HCl
HCl
HO
OCOEt
N
H
Cl
CH3
CH3
(136)
HO
OCOEt
N
H
Cl
CH3
CH3
(137)

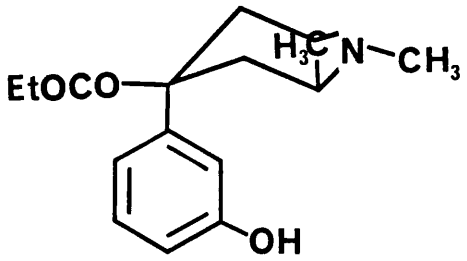
Scheme 38

Treatment of each protected ester with HCl then yielded the corresponding phenolic esters (136) and (137).

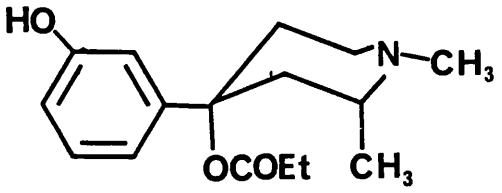
Evidence of the stereochemistry of the two esters (136) and (137) was sought from n.m.r. data. The ^{13}C-n.m.r. spectra of the isomeric esters were too similar for any direct stereochemical deductions to be made from the chemical shifts. The bulk of the stereochemical information was therefore derived from ^{1}H-n.m.r. (see Table 26) and supported with ^{13}C-n.m.r. studies (see Figure 11). The relative configuration of the two isomeric 1,2-dimethyl-4-phenylpiperidin-4-ols and related compounds has been established as c-2-Me, r-4-OR and t-2-Me, r-4-OR for the α- and β-isomers respectively (see section 1.4.2.4.B)[75]. Therefore, the proposed conformation of the two phenolic esters (136) and (137) is (162a) for the β-isomer and either (163a) or (163b) for the α-isomer. The possibility of the conformer (162b) for the β-isomer is discounted on the basis that both the 2-methyl and 4-phenyl are in unfavourable orientations.



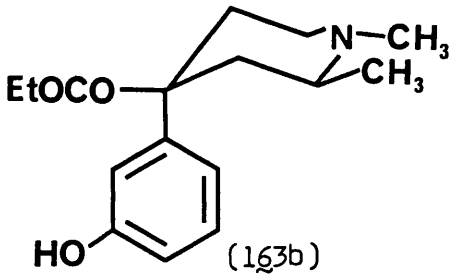
(162a)



(162b)



(163a)



(163b)

Presented below is evidence in support of the conformations (163b) and (162a) for the α- and β-isomers respectively.

The α-isomer was distinguished from the β-isomer by the presence of epimeric conjugate acids in the ^{1}H-n.m.r. spectrum of the hydrochloride salt[82,132] (see page 159).

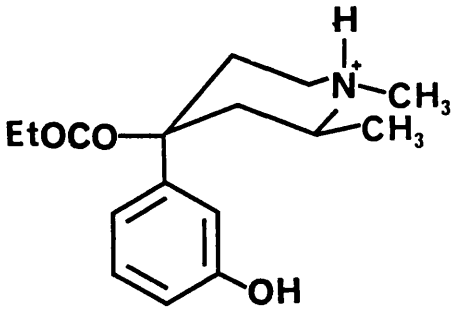
Examination of the ^{1}H-n.m.r. spectrum for the α-isomer (136; base in $CDCl_3$) provides conclusive evidence supporting the conformation (163b). Most of the piperidine ring signals in this spectrum were poorly resolved. However, the resonance at δ2.03 (assigned as the axial C-3-H) displayed two large couplings. The nature of these two large couplings arise from (a) a geminal coupling with the equatorial C-3-H (^{2}J=14.3Hz) and (b) a vicinal coupling with the C-2-H (^{3}J=11.4Hz). The large ^{3}J is indicative of an axial-axial coupling, evidence suggesting that the C-2-H has an axial orientation and therefore the C-2-methyl is equatorially orientated. Hence with a c-2-Me, r-4-OCOEt relative configuration, the 4-aryl group must be axial.

The ^{1}H-n.m.r. spectrum of the β-isomer (137; base in $CDCl_3$) supports an equatorially orientated C-2-methyl, and hence the 4-aryl group must be equatorial, as the relative configuration is t-2-Me, r-4-OCOEt (as in 162a). The resolution of the signals of the piperidine ring carbons was improved compared with the α-isomer and the assignment of the axial C-3-H (δ1.73; ^{2}J=14.3Hz, ^{3}J=11.4Hz), axial C-5-H (δ2.01; ^{2}J=15.7Hz, ^{3}J=15.7Hz, 4.3Hz), and equatorial C-6-H (δ2.78; ^{2}J=11.4Hz, ^{3}J=2.0Hz) was possible. The resonance that provides clear stereochemical information, namely the axial C-3-H, displayed two large couplings, the large ^{3}J being indicative of axial-axial vicinal coupling, supporting an axially orientated C-2-H.

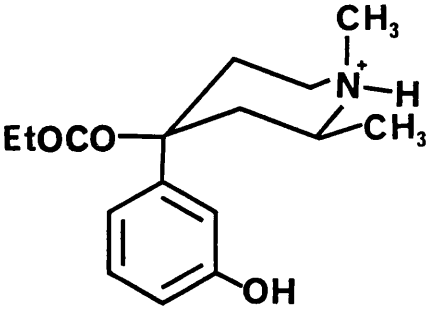
Further evidence of an axially orientated aromatic system in the α-isomer was provided by the chemical shifts of the ester resonances. The $O_2C-CH_2CH_3$ resonances of the α-ester (136) were observed at higher field than those of the β-ester (137). This indicates that the α-ester substituent is shielded by the aromatic group[75]. In the conformation (163b) the preferred plane of the aromatic ring is approximately at right angles to the vertical plane drawn through N-1 and C-4, and in this orientation the $O_2C-CH_2CH_3$ will be shielded as they pass above the plane of the aromatic ring during rotation about the C(4)-O bond[133].

Further evidence for the assigned conformations comes from the ^{1}H-n.m.r. spectra of the hydrochloride salts. The ^{1}H-n.m.r. spectrum of the α-(136) hydrochloride in D_2O, unlike that of the β-salt, gave evidence of the presence of epimeric conjugate acids

which arise as a result of two modes of proton uptake at the basic centre, that is, axial and equatorial protonation[82,132] (see 164).



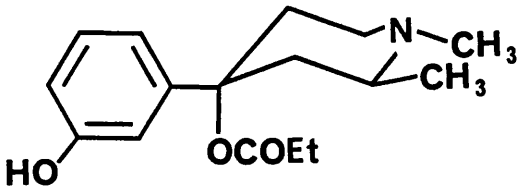
(a) axial protonation



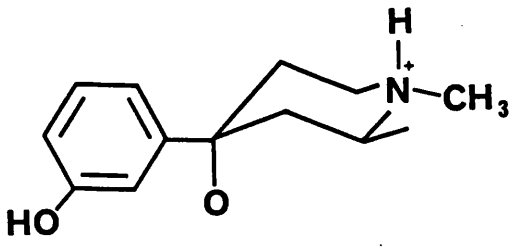
(b) equatorial protonation

(164)

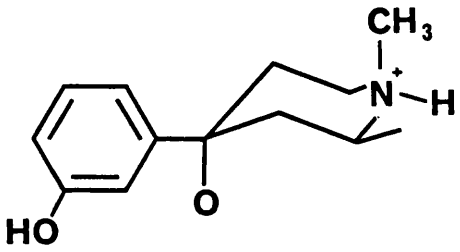
Evidence for the presence of epimeric conjugate acids was indicated by duplication of proton resonances, noticeably the N-CH_3, $OCOCH_2$-, C-2-CH_3 and $OCO-CH_2CH_3$. Epimeric conjugate acids are not anticipated for the β-isomer because equatorial protonation causes additional non-bonded interactions which may not be relieved by a conformational change, as any departure from (162a) places the C-2-methyl and 4-aryl in unfavourable orientations (see 165). Equatorial protonation of the α-isomer (136) can be relieved by a conformational change (see Scheme 39) to an inverted chair (166a) and/or skew-boat (166b) and so relieve non-bonded interactions.



(162a)

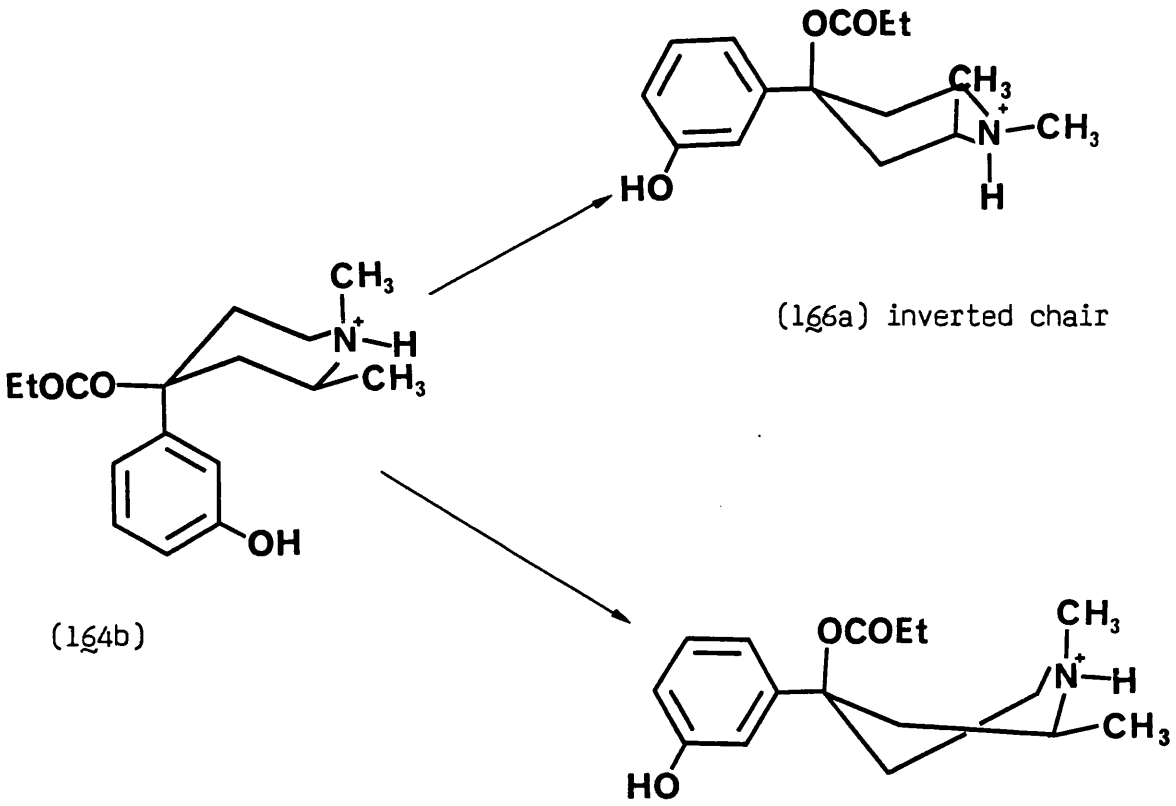


(a) axial protonation



(b) equatorial protonation

(165)



(166a) inverted chair

(164b)

(166b) skew boat

Scheme 39

The conformation of the two epimeric conjugate acids was judged on the basis of the multiplicity of the C-2-H resonance. Irradiation of the C-2-methyl doublet at δ1.37 (major epimer as judged by signal intensity) resulted in the multiplet at δ3.25 reducing to a doublet of doublets (^{3}J=11.0Hz, 2.8Hz). The large coupling was due to axial-axial interaction with the axial C-3-H, while the small ^{3}J was indicative of axial-equatorial coupling with the equatorial C-3-H. This supports an axial C-2-H as in the conformer (164a). A similar procedure repeated on the C-2-methyl of the minor epimer revealed the C-2-H as equatorially orientated (^{3}J=4Hz)

and hence supported the conformation (166a or 166b). The C-2-H resonance of the β-isomer could not be assigned due to signal overlap. However, examination of the resonance signals of the axial and equatorial C-3-H supported an axial C-2-H and hence the conformer (165a).

Examination of the ^{13}C-n.m.r. spectra of the two isomeric esters revealed very small chemical shift differences. Evidence in support of equatorially orientated C-2-methyl in both isomers arises from the similarity of their chemical shift (18.9 ppm for α-, 18.8 ppm for β-). Furthermore, the chemical shifts of the C-4 and C-6 are almost identical, indicating a similar γ-effect by the C-2-methyl[182]. This seems to suggest that the difference in configuration of these two isomers must occur at C-4. The assigned orientation of the aromatic ring in both isomers (axial in α-, equatorial in β-) was supported by the chemical shift difference of the aromatic quaternary carbon (C-1'). In the α-isomer, the C-1' was upfield by 2.3 ppm compared to the chemical shift of C-1' in the β-isomer. This upfield shift is probably due to steric polarization of the axial C-1'[66].

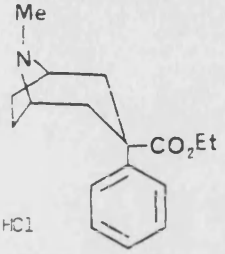
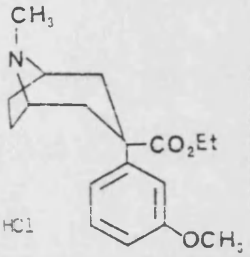
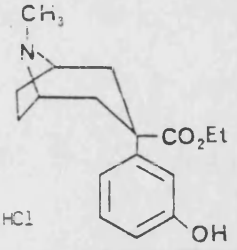
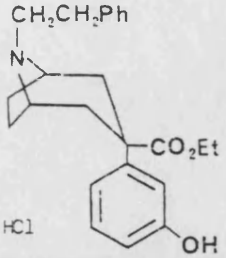
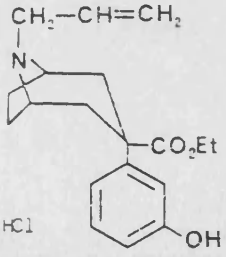
2.4 Pharmacological Evaluation and Concluding Remarks

The 3α-phenolic tropane analogue of pethidine and related structures, and the phenolic α- and β-2-methyl analogues of the reversed ester of pethidine have been synthesised. The compounds 105, 70, 114, 115, 116, 136 and 137 have all been submitted for pharmacological evaluation as either narcotic agonists or antagonists and results received to date are presented in Table 9.

The animal test procedures depend on assessment of the animal's response to a noxious stimulus before and after administration of the test compound. These tests usually give a fair guide to the potency of the drug in man. The interpretation of the pharmacological results presented below is based on the molecular features of the test compounds at the receptor, rather than pharmacokinetic factors such as absorption and transportation of drug molecules.

The phenolic tropane analogue (70) of pethidine displayed feeble agonist activity, a feature that does not support the proposals on ligand-receptor interaction of the 4-phenylpiperidine analgesics (as discussed in Section 2.1, page 56). It is possible to justify this inactivity by consideration of the alignment of the phenolic -OH with the receptor. In morphine the orientation of the phenolic -OH is important for receptor interaction, and is dictated by the rigidity of the molecule. However, in the tropane analogue (70) it is feasible that the bimethylene bridge prevents accurate alignment of this phenolic -OH with the receptor as is possible in the case of morphine (see 167), and hence is responsible for the low

Table 9 ANALGESIC ACTIVITY (ED_{50} mg/Kg SC IN MICE (95% CONFIDENCE LIMIT)) OF SOME TROPANE ANALOGUES OF PETHIDINE

Compound	PHARMACOLOGICAL TEST		
	TAIL-FLICK TEST [a]	TAIL-FLICK ANTAGONIST TEST [b]	PHENYLQUINONE TEST [c]
Morphine Sulphate	5.8 (5.7-5.9)		0.23 (0.20-0.25)
Pethidine Hydrochloride	7.8 (3.0-20.6)		0.8 (0.3-2.2)
Nalorphine Hydrochloride	None at 10	2.6 (0.69-9.75)	0.6 (0.025-1.44)
 67 HCl	4.0 (3.6-4.3)	—	0.5 (0.2-1.7)
 105 HCl	9.8 (6.0-16.0)	—	1.1 (0.2-5.1)
 70 HCl	11% at 30	—	4.5 (1.0-19.3)
 114 HCl	2.5 (1.2-5.2)	—	1.0 (0.5-2.0)
 116 HCl	—	—	7.7 (2.3-26.2)

Notes for Table 9

a. TAIL-FLICK TEST[183]

The procedure involves the application of a thermal stimuli (focused light) to the tail of a mouse for a fixed period of time known to induce a flick of the tail. Following the subcutaneous administration of the potential analgesic agent, the ED_{50} (mg/Kg) can be determined as that dose which inhibits the tail flick in 50% of mice under test.

The tail-flick is one of the most widely used screening tests for potent analgesics. Almost all compounds which are active in the tail-flick test have, when tested, proven to be analgesics in man.

b. TAIL-FLICK ANTAGONISM TEST[184]

The antagonist potency of the compounds prepared was assessed by their ability to block the typical delayed response-time to a thermal stimulus shown by mice medicated with a strong analgesic (morphine). The mice were dosed with the potential antagonist (subcutaneously, mg/Kg) 10 minutes prior to administration of morphine sulphate. The procedure described in the tail-flick test was then undertaken.

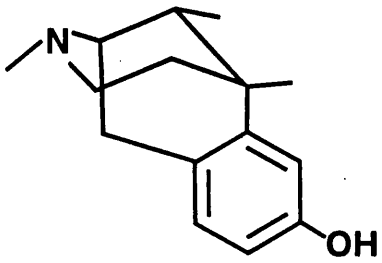
c. PHENYLQUINONE TEST[185]

The intraperitoneal injection of mice with an aqueous solution of phenylquinone elicits a writhing response which is antagonised by analgesic agents (writhing response is characterised by repeated contraction of the abdominal musculature accompanied by extension of the hind limbs).

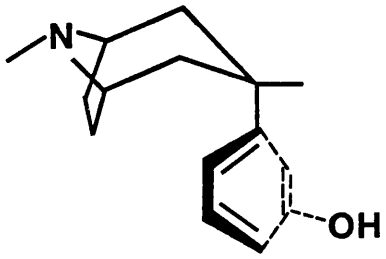
Mice are injected subcutaneously with the compound under test, and then phenylquinone is injected intraperitoneally 20 minutes later. The effective dose (mg/Kg) to inhibit writhing in 50% of the test sample can hence be determined.

activity.

Morphine



Tropane (70)



(PARTIAL FORMULAE)

(167)

The activity displayed by the tropane (67), a non-phenolic derivative, can be explained by the possibility that a significant interaction of the α-phenyl substituent with the aromatic site of the opioid receptor is permitted. This could occur even though the conformation is not appropriate for alignment of a phenolic substituent.

The N-phenethyl tropane analogue (114) displayed approximately 2.5 times the potency of morphine. This potency level may be due to the binding contribution of the N-phenethyl moiety, as it is well known that many, if not all, N-phenethyl analogues of N-methyl ligands have markedly higher potencies than their corresponding parent compounds. Therefore, although the phenolic group will not be ideal for association with the receptor, the presence of an N-phenethyl group may be responsible for the potency level shown.

It is possible that pharmacokinetic factors are responsible for the marked difference in activity between the tropane analogue (70) and its N-phenethyl congerer (114). The lipophilicity associated with the N-phenethyl is much higher than that of an N-methyl group and therefore the difference in activity between the two compounds may be due to greater drug penetration across the blood-brain barrier of (114).

Finally, the N-allyl analogue (116) displayed neither agonist nor antagonist activity (the presence of an N-allyl group in the rigid analgesics confers antagonist properties). It is generally accepted that all potent opioid antagonists are phenolic derivatives. Therefore, to be an antagonist the ligand must interact with the phenolic site of the receptor. From the interpretation of the inactivity of the phenolic analogue (70), it is suggested that in the phenolic tropanes the association with the receptor of the -OH is poor. Hence, the absence of antagonist properties in the N-allyl analogue may be understood.

Analgesic potency results on α- and β-2-methyl analogues of the reversed ester of pethidine were not yet available at the time of writing this thesis. In the α-2-methyl analogue (136) syn diaxial non-bonded interactions which act against optimum aryl conformation in regard to phenolic association with the receptor should be much less than those obtained in the tropane analogue. Hence, these results are required before conclusive deductions can be drawn on ligand-receptor interaction of phenolic 4-phenylpiperidines.

3. EXPERIMENTAL

3.1 Introduction

^{1}H-n.m.r. spectra were recorded on a JEOL GX270 MHz Fourier Transform (FT) NMR Spectrometer unless otherwise stated. The following abbreviations are used to describe resonance appearance in the ^{1}H-n.m.r. spectra: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m.

^{13}C-n.m.r. spectra were recorded on a JEOL GX270 FT NMR Spectrometer operating at 67.8 MHz unless otherwise stated. The multiplicity of the resonances was obtained from DEPT (Distortionless Enhancement by Polarisation Transfer) and INEPT (Insensitive Nuclei Enhanced by Polarisation Transfer) spectra in which the phase of the signal indicated the number of protons attached to the carbon atom giving rise to that signal.

The Infra-red spectra (liquids as films, solids as KBr discs or Nujol mulls) were recorded on a Unicam SP1025 Spectrometer.

Mass spectra were measured on a VG Micromass 7070E Mass Spectrometer operating at 70 EV EI.

Elemental analyses were carried out by Butterworth Laboratories Ltd., Middlesex.

Melting points were recorded on a Gallenkamp apparatus, and are uncorrected.

Optical rotation readings were recorded on an Optical Activity Ltd., AA-10 Polarimeter.

3.2 Ancillary Chemicals

3.2.1 Phenyl vinyl ketone (118)

Dimethylamine hydrochloride (30g), paraformaldehyde (14g) and acetophenone (44g) were dissolved in ethanol (160ml), and concentrated hydrochloric acid (0.8ml) added. The resulting solution was refluxed for 3 hours and allowed to cool to room temperature to give N,N-dimethyl-2-benzoylethylamine hydrochloride as a white crystalline precipitate (40g; 51%), m.p. 152°C (Lit.,[186] m.p. 156°C). The precipitate was dissolved in K_2CO_3 solution (40%; 200ml), extracted with ether (3 x 100ml), dried ($MgSO_4$) and evaporated to give N,N-dimethyl-2-benzoylethylamine as a clear oil.

ν max : 1700cm^{-1} (C=Ostr)

δ_H ($CDCl_3$; free base):

1.80 (6H; s; 2xN-CH_3), 2.31 (2H; t, ^3J 6.5Hz; CH_2 -N), 2.69 (2H; t, ^3J 6.5Hz; CH_2-COPh), 6.94-7.07 (3H; m; Ar-H), 7.50-7.53 (2H; m; Ar-H).

δ_C ($CDCl_3$; free base):

35.68 (CH_2-COPh), 44.36 (2 x N-CH_3), 53.29 (CH_2-NMe_2), 126.89 (Ar-3'; Ar-5'), 127.43 (Ar-2'; Ar-6'), 131.78 (Ar-4'), 135.88 (Ar-1'), 197.37 (C=O).

m/z (Low EV.EI):

M^+ 177 (7%), 58 (100%)

N,N-Dimethyl-2-benzoylethylamine (25g) was dissolved in acetone (250ml), and methyl iodide (25ml) added. The white precipitate produced was left standing at room temperature for 3 hours. The precipitate was filtered off and washed with acetone (2 x 50ml) to give N,N-dimethyl-2-benzoylethylamine methiodide (28g; 62%), m.p. 200°C (Lit.,[187] m.p. 212°C, from water).

The methiodide (4.0g) was suspended in K_2CO_3 solution (10%; 50ml) and extracted with ether (4 x 100ml). The ether extract was washed with water (2 x 50ml), dried ($MgSO_4$) and evaporated *in vacuo* to give phenyl vinyl ketone (1.6g; 96%) as a clear oil with a characteristic sweet odour, sufficiently pure for subsequent use.

δ_C ($CDCl_3$):
128.27 (Ar-3'; Ar-5'; $\underline{C}H_2$=CH-), 129.68 (-$\underline{C}$H=CH_2), 131.94 (Ar-4'), 132.63 (Ar-2'; Ar-6'), 136.87 (Ar-1'), 190.38 ($\underline{C}$=O)

3.2.2 3-(2-Tetrahydropyranyloxy)bromobenzene (157)

3-Bromophenol (25g) was added dropwise to stirred, ice-cooled dihydropyran (50g) containing a few drops of hydrochloric acid. The mixture was stirred for an additional 1.5 hours at room temperature, after which it was diluted with ether (75ml). The ethereal mixture was washed with NaOH (10%; 2 x 25ml), water (2 x 25ml) and then dried ($MgSO_4$). Evaporation of the solvent left a residue which solidified on refrigeration. Recrystallisation from n-hexane afforded the pure, colourless crystals of 3-(2-tetrahydropyranyloxy)bromobenzene (14.3g; 38%), m.p. 37°C (Lit.,[57] m.p. 39-40°C; Lit.,[181] reported an oil).

ν max : no characteristic signal.

δ_H ($CDCl_3$):

1.49-1.97 (6H; m; O-CH_2-$\underline{CH}_2$-$\underline{CH}_2$-$\underline{CH}_2$-CH), 3.52-3.58 (1H; m; O-$\underline{CH}$-CH_2), 3.75-3.84 (1H; m; O-$\underline{CH}$-CH_2), 5.33 (1H; t, ^3J 2Hz; O-$\underline{CH}$-O), 6.91-7.22 (4H; m; Ar-$\underline{H}$).

δ_C ($CDCl_3$):

18.52 ($CH_2\underline{C}H_2CH_2CH$), 25.15 (O-$CH_2\underline{C}H_2$), 30.19 (O-CH-$\underline{C}H_2$), 61.69 (O-$\underline{C}H_2$), 96.23 (O-$\underline{C}$H), 115.2 (Ar-4'), 119.8 (Ar-2'), 122.6 (Ar-1'), 124.5 (Ar-6'), 130.4 (Ar-5'), 157.9 (Ar-3').

m/z :

$M^{\dot{+}}$ 256: 258 (6 : 6.2%), 85 (100%).

3.2.3 (+)-3'-Nitrotartranilic acid (145)

A solution of 3-nitroaniline (8.0g) and (+)-tartaric acid (8.6g) in dry tetrahydrofuran (200ml) was allowed to stand under N_2 for 18 hours at 25°C in the presence of dicyclohexylcarbodiimide (13g). The dicyclohexylurea which formed was removed by filtration, and the filtrate made basic with NaOH (10%) and extracted with benzene (3 x 25ml). The basic solution was acidified with HCl (5%) and on cooling gave the tartranilate. Recrystallisation from water and drying gave pure (+)-3'-nitrotartranilic acid (5.4g; 35%) m.p. 209°C (Lit.,[92] 207-208°C); $[\alpha]_D^{23}$ = +92.0° (c 0.5, MeOH)

ν max : 3300-3450 cm^{-1} (OH str), 1730 cm^{-1} (C=O str of -COOH), 1680 cm^{-1} (C=O str of -CONH).

δ_H (DMSO-d6) :

4.47 (1H; d, ^{3}J 3Hz; C<u>H</u>-COOH), 4.48 (1H; d, ^{3}J 3Hz C<u>H</u>CONH), 7.62 (1H; m; Ar-5'<u>H</u>), 7.92 (1H; m; Ar-6'<u>H</u>), 8.10 (1H; m; Ar-4'<u>H</u>), 8.83 (1H; m; Ar-2'<u>H</u>), 10.24 (1H; s; COO<u>H</u>).

δ_C (DMSO-d6)

72.39 (<u>C</u>H-COOH), 73.85 (<u>C</u>H-CONH), 114.0 (Ar-2'), 118.31 (Ar-4'), 126.03 (Ar-6'), 130.25 (Ar-5'), 139.88 (Ar-1'), 148.12 (Ar-3'), 171.81 (<u>C</u>ONH), 174.00 (<u>C</u>OOH).

m/z (Low EV.EI) :

$M^{\dot{+}}$ 270 (25%), 252 (18%), 138 (100%), 92 (30%).

3.3 The Tropanes

3.3.1 Methyl meso-αα'-dibromoadipate (73)

A mixture of adipic acid (100g) and thionyl chloride (200g) was heated and stirred until complete solution occurred and the evolution of hydrogen chloride ceased. The excess thionyl chloride was removed *in vacuo*. A portion of the resulting acid chloride (10g) was treated with dry bromine (20g). The resulting solution was heated and stirred an additional 2 hours, and then added cautiously to methanol (50ml), while the temperature was maintained below 10°C. It was then stirred at room temperature overnight. The excess methanol was removed by evaporation *in vacuo* and the oily residue dissolved in ether (50ml). The ether layer was washed with sodium bisulphite (2%; 2 x 50ml), sodium carbonate (3%; 2 x 100ml) and then water (3 x 100ml), dried ($MgSO_4$) and evaporated *in vacuo* to give methyl meso-αα'-dibromoadipate as a white semi-solid (6.0g; 33%). This semi-solid was induced to solidify by the addition of petroleum spirit (b.p. 60-80°C) and had m.p. 73°C (Lit.,[100] m.p. 74-76°C).

ν max : 1745 cm^{-1} (C=O str)

δ_H ($CDCl_3$; recorded on a JEOL J.N.M.-PMX 60 NMR Spectrometer operating at 60 MHz):

2.10-2.46 (4H; m; $C\underline{H}_2$-$C\underline{H}_2$), 3.81 (6H; s, 2 x $OC\underline{H}_3$), 4.16-4.36 (2H; m; 2 x $C\underline{H}Br$).

δ_C ($CDCl_3$; recorded on a JEOL FX90X F.T. NMR Spectrometer operating at 22.5 MHz):

32.45 ($\underline{C}H_2$-$\underline{C}H_2$), 44.26 (2 x $\underline{C}$H-Br), 53.15 (2 x O$\underline{C}H_3$), 169.6 (2 x $\underline{C}$=O).

$^m/_z$: M^+ 330 (1.6%) : 332 (3.0%) : 334 (1.4%).

3.3.2 cis - 2,5-Dicarbomethoxy-N-benzylpyrrolidine (76) and trans-2,5-Dicarbomethoxy-N-benzylpyrrolidine (77)

A solution of methyl meso-αα'-dibromoadipate (73; 100g) in toluene (300ml) was heated to reflux, heating was then discontinued, and benzylamine (100g) added at a rate sufficient to maintain modest reflux (approximately 1 hour). At the end of the addition the reaction mixture was refluxed for 24 hours. The solution was cooled and the solid benzylamine hydrobromide filtered off. The filtrate was washed with water (2 x 50ml), dried ($MgSO_4$) and evaporated in vacuo. The resultant oil was dissolved in dry ether (200ml) and treated with ethereal-HCl. The solid produced was filtered, dried and recrystallised from acetone to give cis-2,5-dicarbomethoxy-N-benzylpyrrolidine hydrochloride (49g; 52%), m.p. 122°C. The mother liquors were reduced in volume under reduced pressure and allowed to cool, yielding a mixture of cis and trans-2,5-dicarbomethoxy-N-benzylpyrrolidine hydrochloride. This mixture was removed by filtration, the filtrate was evaporated in vacuo to dryness and the residue was recrystallised from ethyl acetate to give pure trans-2,5-dicarbomethoxy-N-benzylpyrrolidine hydrochloride (1.4g; 1.5%), m.p. 113°C.

cis-2,5-dicarbomethoxy-N-benzylpyrrolidine (76)

ν max : 1750 cm^{-1} (C=O str), 760, 710 cm^{-1} (monosub. benzene).

δ_H : see table 10, No.1

δ_C : see table 11, No.1

Found : C, 57.20; H, 6.53; N, 4.49%

$C_{15}H_{20}NO_4Cl$ requires: C, 57.41; H, 6.38; N, 4.46%

m/z : see table 12

trans-2,5-dicarbomethoxy-N-benzylpyrrolidine (77)

ν max : 1750 cm^{-1} (C=O str), 770, 710 cm^{-1} (monosub. benzene).

δ_H : see table 10, No.2

δ_C : see table 11, No.2

Found : C, 57.13; H, 6.59; N, 4.43%

$C_{15}H_{20}NO_4Cl$ requires: C, 57.41; H, 6.38; N, 4.46%

m/z : see table 12

3.3.3 cis-N-Benzyl-2,5-bis(hydroxymethyl)pyrrolidine (78)

A solution of cis-2,5-dicarbomethoxy-N-benzylpyrrolidine (76; 62g) in dry tetrahydrofuran (300ml) was added slowly, with stirring, to a suspension of $LiAlH_4$ (18.6g) in dry tetrahydrofuran (250ml) at 0°C. The mixture was stirred and refluxed for 1 hour, cooled to 0-5°C and then cautiously treated with water (300ml). After standing for 1 hour at room temperature the solid material was filtered off. The filtrate was washed with water (2 x 50ml), dried ($MgSO_4$) and evaporated in vacuo to yield cis-N-benzyl-2,5-bis-

(hydroxymethyl)pyrrolidine as a light yellow oil. Treatment of this oil with ethereal-HCl gave the hydrochloride (44g; 76%) m.p. 121°C (Lit.,[109] m.p. 118-120°C).

ν max : 3500-2300 cm^{-1} (OH str, $\overset{+}{N}H$ str); 780, 720 cm^{-1} (monosub. benzene).

δ_H : see table 10, No.3

δ_C : see table 11, No.3

m/z : see table 12

3.3.4 cis-N-Benzyl-2,5-bis(chloromethyl)pyrrolidine (72)

Thionyl chloride (76g) was added, with stirring, to a suspension of cis-N-benzyl-2,5-bis(hydroxymethyl)pyrrolidine (78; 47g) in dry toluene (300ml). The mixture was stirred for 2 hours at room temperature, and for an additional hour at 50°C, until complete solution occurred and the evolution of hydrogen chloride ceased. Dry ether (300ml) was added and a solid precipitated. This solid was collected by filtration, washed with dry ether (2 x 50ml), dried and then recrystallised from isopropanol to give cis-N-benzyl-2,5-bis(chloromethyl)pyrrolidine hydrochloride (33g; 53%) m.p. 164°C (Lit.,[108] m.p. 163-164°C).

ν max : 1600 cm^{-1} (C . . . C str); 760, 710 cm^{-1} (monosub. benzene)

δ_H : see table 10, No.4

δ_C : see table 11, No.4

m/z : see table 12

3.3.5 cis-N-Benzyl-2,5-bis(iodomethyl)pyrrolidine (82)

A mixture of anhydrous sodium iodide (1.7g) and dry acetone (100ml) was heated on a steam bath for 1 hour. cis-N-Benzyl-2,5-bis (chloromethyl)pyrrolidine (72; 2g) was then added and heating maintained for 24 hours. The mixture was cooled to room temperature, and the solid filtered off. The filtrate was concentrated in vacuo and chloroform (50ml) was added. The chloroform was washed with sodium bisulphite (10%; 2 x 100ml), sodium hydrogen carbonate (5%; 50ml) and then water (2 x 50ml), dried ($MgSO_4$) and evaporated under reduced pressure to yield cis-N-benzyl-2,5-bis(iodomethyl)pyrrolidine as a yellow oil (1.6g; 48%).

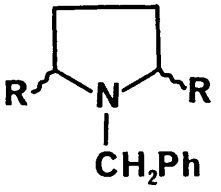
ν max : 760, 710 cm^{-1} (monosub. benzene)

δ_H : see table 10, No.5

δ_C : see table 11, No.5

Table 10

^{1}H-N.M.R. CHARACTERISTICS OF SOME N-BENZYLPYRROLIDINES [a]



No.	Compound	Isomer Designation	R	N-CH_2-	H_2H_5	H_3H_4	Other Protons
1	b ~76	cis	CO_2CH_3	δ3.90,s	δ3.42,m	δ2.05,m	OCH_3 δ3.56, s Aryl-H δ7.19-7.31,m
2	b ~77	trans	CO_2CH_3	e	δ3.83,m	δ1.91,m δ2.30,m	OCH_3 δ3.63, s Aryl-H δ7.20-7.31,m
3	c ~78	cis	CH_2OH	δ3.73,s	δ3.37,m	δ1.73,t	2 x CH_2OH δ2.87-3.40,m Aryl-H δ7.14-7.23,m
4	d ~72	cis	CH_2Cl	δ4.56,s	δ3.75 broad s	δ2.13-2.36,m	2 x CH_2Cl δ4.05,m Aryl-H δ7.30-7.70,m
5	c ~82	cis	CH_2I	δ3.70,s	δ2.93,s	δ2.60-2.80,m	2 x CH_2I δ1.60-2.10,m Aryl-H δ7.20,m

Notes to Table 10

a. Spectra recorded in $CDCl_3$ with internal tetramethylsilane, δ values (in ppm) refer to centres of resonance signals and hence represent only approximate chemical shifts in most cases.

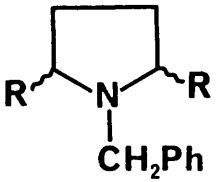
b. Spectra were recorded on a Brucker WH-400 NMR Spectrometer operating at 400 MHz.

c. Spectra were recorded on a JEOL J.N.M.-PMX60 NMR Spectrometer operating at 60 MHz.

d. As hydrochloride salt.

e. Signal appears as an AB quartet; δ3.95 for one proton and δ3.78 for the other; ^2J = 13Hz.

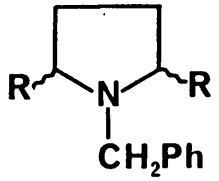
Table 11 ^{13}C-N.M.R. CHARACTERISTICS OF SOME N-BENZYLPYRROLIDINES [a]



No.	Compound	Isomer Designation	R	^{13}C Chemical Shifts (ppm; TMS internal standard)							Other carbons
				N-$\underline{C}H_2$	C - 2 - 5	C - 3 - 4	Aromatic C				
							Cq	Co	Cm	Cp	
1	76	cis	CO_2CH_3	59.92	67.61	30.82	139.6	131.8	130.2	129.4	O_2-$\underline{C}H_3$: 53.80 $\underline{C}$=O : 175.9
2	77	trans	CO_2CH_3	54.07	63.38	28.39	138.6	129.0	128.2	127.1	O_2-$\underline{C}H_3$: 51.36 $\underline{C}$ = O : 174.4
3	78	cis	CH_2OH	58.29	65.88	27.19	139.4	129.1	128.4	127.3	$\underline{C}H_2OH$: 63.54
4	72	cis	CH_2Cl	58.02	65.93	27.25	138.6	127.6	127.4	126.3	$\underline{C}H_2Cl$: 46.59
5	82	cis	CH_2I	57.91	66.79	26.71	139.2	128.7	128.3	127.3	$\underline{C}H_2I$: 30.28

a. Spectra were recorded on a J.E.O.L. FX90X Fourier Transform N.M.R. Spectrometer operating at 22.5 MHz; bases in $CDCl_3$

Table 12 PERCENT ABUNDANCE OF DIAGNOSTIC FRAGMENT IONS OF SOME N-BENZYLPYRROLIDINES [a]



Compound	Isomer Designation	R	M + 1	Ion Types [b]					
				A	B	C	D	E	F
76	cis	CO_2CH_3	100	58	17	27	37	8	-
77	trans	CO_2CH_3	97	55	22	100	42	17	-
78	cis	CH_2OH	80	38	23	100	37	13	27
72	cis	CH_2Cl	d	100[c] (31)	23[c] (7)	28	85	13	93[c] (36)

a. Spectra recorded on ISO.BUT (CI) programme.

b. Ion types are: A B C D E F

c. Values in parentheses represent fragment abundance of ion containing high atomic weight isotope.

d. M+1 for 72; 258 (47%) : 260 (28%) : 262 (5%).

3.3.6 Methyl 3β-hydroxy-8-methyl-8-azabicyclo[3,2,1] octane-3α-carboxylate

(α-Ecgonine methyl ester; 90)

A saturated aqueous solution of potassium cyanide (18g) was added to a saturated aqueous solution of tropan-3-one hydrochloride (40g) while the temperature was maintained below 10°C. The white slurry was stirred at room temperature for 30 minutes, filtered, and the resulting crude cyanohydrin washed with water (100ml), ethanol (75ml) and ether (100ml), and then dried *in vacuo*. The cake was added portionwise to 500ml of concentrated hydrochloric acid with stirring while the temperature of the acid was kept below 25°C. The resulting mixture was heated on a water bath at 80°C for 48 hours and then evaporated to dryness under reduced pressure. The crude α-ecgonine hydrochloride was dried by azeotropic distillation with toluene. The solid was added to 750ml of methanol saturated with dry hydrogen chloride, and refluxed for 20 hours. The solvent was evaporated *in vacuo*, the residue dissolved in water (150ml) and filtered. The filtrate was made basic with potassium carbonate and extracted with chloroform (4 x 200ml). The combined extracts were washed with water (2 x 50ml), dried ($MgSO_4$) and evaporated *in vacuo* to give α-ecgonine methyl ester (26g; 57%), m.p. 112-113°C (Lit.,[129] m.p. 114°C).

ν max : 2500-3300 cm^{-1} (OH str), 1710-1770 cm^{-1} (C=O str)

δ_H : see table 13, No.1

δ_C : see table 14, No.1

m/z : see table 17

3.3.7 3β-Hydroxy-3α-bis(3-methoxyphenyl)hydroxymethyl-8-methyl-8-azabicyclo[3,2,1]octane

(3α-Bis(metamethoxyphenyl)hydroxymethyl-3β-tropanol; 96)

α-Ecgonine methyl ester (90; 8.0g) was heated under reflux for 90 minutes with the Grignard reagent prepared from 3-bromoanisole (56.8g) and magnesium (8.0g) in dry tetrahydrofuran (200ml). The solution was then stirred at room temperature overnight. The cooled product was then poured onto ice and acetic acid (50ml) and extracted with ether (3 x 50ml). The aqueous layer was basified with strong aqueous ammonia and extracted with chloroform (3 x 100ml). The combined chloroform extracts were washed with water (2 x 50ml), dried ($MgSO_4$) and evaporated to give 3β-hydroxy-3α- bis(3-methoxyphenyl)hydroxymethyl -8-methyl-8-azabicyclo[3,2,1]octane (13.8g; 90%) as a light yellow oil. Treatment of this oil with ethereal-HCl gave the hydrochloride, m.p. 239-241°C (acetone).

ν max : 3150-3400cm^{-1} (OH str),

δ_H : see table 13, No.2

δ_C : see table 13, Nos. 2 and 3

Found : C, 65.79; H, 7.39; N, 3.21%

$C_{23}H_{30}NO_4Cl$ requires : C, 65.79; H, 7.16; N, 3.34%

m/z : see table 17

3.3.8 3β-(3-Methoxybenzoyl)-3α-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]octane

(3α-(3-Methoxyphenyl)-3β-tropanyl(3-methoxyphenyl) ketone; 99)

A suspension of the diol hydrochloride (96-HCl; 10g) and fused powdered zinc chloride (30g) in acetic anhydride (30ml) was stirred for 24 hours at room temperature (solution complete within 40 minutes). It was poured into a solution of sodium hydroxide in water (15%; 400ml) and then extracted with chloroform (5 x 200ml). The chloroform was washed with water (3 x 100ml), dried ($MgSO_4$) and evaporated to yield the title compound as a dark brown oil (7.5g; 86%).

ν max : 1780 cm^{-1} (C=O str)

δ_C : see table 14, No.4

m/z : see table 17

3.3.9 3β-(3-Methoxybenzoyl)-3α-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]octane oxime hydrochloride

(3α-(3-Methoxyphenyl)-3β-tropanyl(3-methoxyphenyl)ketoxime hydrochloride; 101)

A mixture of 3β-(3-methoxybenzoyl)-3α-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]octane (99; 10g), hydroxylamine hydrochloride (8.0g), pyridine (50ml) and propan-1-ol (200ml) was refluxed for 16 hours. On cooling a solid was deposited which was filtered off and washed with water. The resulting solid was dried and recrystallised from water to give 3β-(3-methoxybenzoyl)-3α-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]octane oxime hydro-

chloride (4.2g; 37%), m.p. 280-282°C.

ν max : 3150-3500 cm^{-1} (OHstr)

δ_H : see table 13, No.3

δ_C : see table 14, No.5

Found : C, 62.98; H, 7.22; N, 6.38%

$C_{23}H_{29}N_2O_3Cl.H_2O$ requires : C, 63.50; H, 7.13; N, 6.44%

$^m/_z$: see table 17

3.3.10 3α-(3-Methoxyphenyl)-8-methyl-8-azabicyclo [3,2,1] octane-3β-carboxylic acid hydrochloride

(3α-(3-Methoxyphenyl)-3β-tropane carboxylic acid hydrochloride; 1Q3)

Dry hydrogen chloride was passed into a suspension of 3β-(3-methoxybenzoyl)-3α-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1] octane oxime hydrochloride (1Q1; 10g) in glacial acetic acid (100ml). After a few minutes, complete solution occurred and the whole was heated on a steam bath while hydrogen chloride was slowly passed into the solution. After 2 hours the solution was evaporated to dryness under reduced pressure. The crystalline residue was boiled with acetone to yield the amino acid hydrochloride (3.6g; 48%), m.p. 210°C (methanol-ether).

ν max : 2500-3000 cm^{-1} (OHstr), 1730 cm^{-1} (C=Ostr)

δ_H : see table 13, No.4

δ_C : see table 14, No.6

Found : C, 61.48; H, 7.36; N, 4.18%

$C_{16}H_{22}NO_3Cl$ requires: C, 61.63; H, 7.07; N, 4.50%

m/z : see table 17

3.3.11 Ethyl 3α-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1] octane-3β-carboxylate hydrochloride

(Ethyl 3α-(3-methoxyphenyl)-3β-tropane carboxylate hydrochloride; 105)

A solution of 3α-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1] octane-3β-carboxylic acid hydrochloride (103; 10g) in absolute ethanol (200ml) saturated with dry hydrogen chloride was refluxed for 24 hours. Evaporation to dryness gave a crystalline solid which was recrystallised from ethanol-ether to give the title compound (6.3g; 58%), m.p. 135°C.

ν max : 1710-1750 cm^{-1} (C=Ostr)

δ_H : see table 13, No.5

δ_C : see table 14, No.7

Found : C, 61.01; H, 7.96; N, 3.80%

$C_{18}H_{26}NO_3Cl.H_2O$ requires : C, 60.67; H, 7.56; N, 3.92%

m/z : see table 17

3.3.12 Ethyl 3α-(3-hydroxyphenyl)-8-methyl-8-azabicyclo[3,2,1] octane-3β-carboxylate

(Ethyl 3α-(3-hydroxyphenyl)-3β-tropane carboxylate; 70) Boron tribromide in dichloromethane (1.0M; 10ml) was added to a solution of ethyl 3α-(3-methoxyphenyl)-8-methyl-8-azabicyclo 3,2,1 octane-3β-carboxylate (105, as base; 1.0g) in dry chloroform (5ml). The mixture was stirred at room temperature for 2 hours, and then poured onto a mixture of ice and ammonia. The liberated free base was extracted with chloroform (3 x 50ml), the combined chloroform extracts were dried ($MgSO_4$) and evaporated *in vacuo* to yield a light brown oil. Treatment of the oil with ethereal-HCl, and subsequent crystallisation of the resulting solid from ethanol, gave ethyl 3α-(3-hydroxyphenyl)-3β-tropane carboxylate hydrochloride (0.45g; 41%), m.p. 208-209°C.

ν max : 3200-3300 cm^{-1} (OHstr), 1740 cm^{-1} (C=Ostr)

δ_H : see table 13, Nos. 6 and 7

δ_C : see table 14, No.8

Found : C, 62.92; H, 7.62; N, 4.15%

$C_{17}H_{24}NO_3Cl$ requires : C, 62.67; H, 7.37; N, 4.30%

$^m/_z$: see table 17

Table 13 ^{1}H-N.M.R. CHARACTERISTICS OF SOME 3,3-DISUBSTITUTED TROPANES[a]

No.	Compound	N-CH_3	1(5)H[b]	2(4)H	6(7)H	Other Protons
1	90 in $CDCl_3$	δ2.24,s	δ3.22, $W_{½}$ 16	α: δ2.09[c] β: δ2.30 ^{2}J14, ^{3}J7	δ1.55[d], 1.95[e]	OH δ5.50, broad s CO_2CH_3 δ3.76, s
2	96 HCl in D_2O[l]	δ2.64,s	δ3.80, $W_{½}$ 17	δ 2.21-2.34[f]	δ1.87[d], 2.11[e]	OCH_3 δ3.70, s Aryl-H δ6.85, 7.21[g]
3	101 in $CDCl_3$ (as base)	δ2.17,s	δ3.22, $W_{½}$ 11	β: δ3.05[h] ^{2}J14 α: δ2.44[h] ^{2}J16	δ1.65[e], 1.34[d]	2x OCH_3 δ3.57, 3.76, s Aryl-H δ6.14-7.24, m N-OH δ5.82, broad s
4	103 in D_2O	δ2.68,s	δ3.93, $W_{½}$ 11	β: δ2.53[h] ^{2}J16 α: δ3.09[h] ^{2}J16	δ1.59[d], 1.89[i]	OCH_3 δ3.78, s Aryl-H δ6.95, 7.22, 7.33[j]
5	105 in $CDCl_3$ (as base)	δ2.16,s	δ3.19, $W_{½}$ 16	β: δ3.06 ^{2}J14, ^{3}J7 α: δ1.81[e] ^{2}J14	δ1.38[d], 1.96[i]	OCH_2 δ4.05, q, ^{3}J7 OCH_3 δ3.78, s CH_2CH_3 δ1.18, t, ^{3}J7 Aryl-H δ6.74, 7.03, 7.23[k]
6	70 in $CDCl_3$	δ2.22,s	δ3.23, $W_{½}$ 12	β: δ2.82 ^{2}J14, ^{3}J6 α: δ2.10[e] ^{2}J14	δ1.41[d], 1.85[i]	Aryl-OH δ8.20, broad s OCH_2 δ4.01 q, ^{3}J7 CH_2CH_3 δ1.10, t, ^{3}J7 Aryl-H δ6.68, 7.07[g]
7	70 HCl in D_2O[m]	δ2.75,s	δ3.99, $W_{½}$ 8	β: δ3.16 ^{2}J15 α: δ2.58 ^{2}J15	δ1.67[d], 2.00[e]	OCH_2 δ4.02, q, ^{3}J6.9 CH_2CH_3 δ1.06 t, ^{3}J6.9 Aryl-H δ6.85, 7.20 7.34

Notes to Table 13

a. δ values refer to centres of resonance signals and hence represent only approximate chemical shifts in most cases. J (approx) and $W_{\frac{1}{2}}$ values are given in Hz.

b. Unresolved, near-symmetrical multiplet.

c. Narrow multiplet.

d. 2-Proton multiplet with two prominent lines.

e. 2-Proton signal of two broad lines.

f. 4-Proton multiplet (poorly resolved).

g. Multiplets, higher 1 and lower field 3 proton intensity.

h. 2-Proton signal with two prominent lines.

i. 2-Proton multiplet.

j. Multiplets, higher 1, middle 1 and lower field 2 proton intensity.

k. Multiplets, higher 1, middle 2 and lower field 1 proton intensity.

l. Spectrum recorded on a JEOL GX 400 MHz FT NMR Spectrometer.

m. Spectrum recorded on a Brucker WH-400 MHz NMR Spectrometer.

Table 14

^{13}C-N.M.R. CHARACTERISTICS OF SOME 3,3-DISUBSTITUTED TROPANES[a]

No.	Compound	Solvent	^{13}C Chemical Shifts (ppm; TMS Int. Standard)													
			N-CH$_3$	C-1 -5	C-2 -4	C-6 -7	C-3	C=O or C=N or -C-OH	O-CH$_3$	Aromatic C						Ester CH$_2$/ CH$_3$
										C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	
1	90	CDCl$_3$	39.30	58.42	41.77	27.27	71.55	174.6								52.35
2	96[b]	CDCl$_3$	39.98	58.78	41.82	28.88	(75.8)	(75.8)	55.04	146.4	111.5	158.7	114.6	128.1	120.7	
3	96[b]	MeOH	40.36	60.19	42.64	29.53	(77.36)	(80.50)	55.53	148.2	112.5	160.0	115.8	128.7	122.1	
4	99[b]	CDCl$_3$	39.28	57.97	44.48	29.04	50.23	173.8	54.82 (54.82)	143.3 (142.7)	112.3 (111.8)	159.5 (158.7)	115.1 (113.2)	129.1 (128.3)	119.3 (119.3)	
5	101[b]	CDCl$_3$ + DMSO	39.49	60.89	37.59	24.00	44.21	162.7	55.15 (54.72)	144.8 (135.7)	113.4 (111.0)	158.9 (158.4)	115.0 (113.4)	128.2 (128.0)	120.8 (120.8)	
6	103[b]	DMSO	e	60.00	32.50	21.06	42.62	173.4	53.50	139.3	110.2	157.6	121.1	127.5	117.4	
7	105[b,c]	CDCl$_3$	39.33	59.10	40.52	27.63	45.83	174.9	54.99	143.8	111.5	159.4	113.3	128.9	119.1	60.35[d] 14.14
8	70	CDCl$_3$	38.97	59.18	38.64	26.74	45.67	175.8		143.4	114.2	156.8	114.5	129.0	118.0	60.78[d] 13.99

a. Values in parentheses may be interchanged.

b. Spectra were recorded on a J.E.O.L. FX 90X Fourier Transform N.M.R. Spectrometer operating at 22.5 Mhz.

c. As base.

d. High field resonance (CH$_3$). Low field resonance (CH$_2$).

e. Signal not seen due to low concentration.

3.3.13 Ethyl 3α-(3-methoxyphenyl)-8-azabicyclo[3,2,1]octane-3β-carboxylate

(Ethyl 3α-(3-methoxyphenyl)-3β-nortropane carboxylate; 108)

Ethyl 3α-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]octane-3β-carboxylate (105, as base; 5.0g) and trichloroethylchloroformate (6.0g) were dissolved in dry toluene (100ml), and anhydrous potassium carbonate (2.0g) was added. The mixture was refluxed for 2 days, cooled and ether added (200ml). The resulting solution was washed with NaOH (5N, 2 x 80ml) and then with water (3 x 50ml). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give a gum. The excess trichloroethylchloroformate was removed in vacuo to give a white solid. This white solid, in acetic acid (90%, 150ml), was treated with powdered zinc (1.5g) and the mixture stirred at room temperature for 16 hours. The mixture was basified with ammonia and extracted with chloroform (4 x 250ml). The combined chloroform extracts were washed with water (2 x 50ml), dried ($MgSO_4$) and evaporated in vacuo to yield ethyl 3α-(3-methoxyphenyl)-8-azabicyclo[3,2,1]octane-3β-carboxylate as a light brown gum. Treatment of this gum with ethereal-HCl gave the hydrochloride (3.2g; 60%), m.p. 201-204°C (ethanol).

ν max : 3340 cm^{-1} (N-H str), 1730 cm^{-1} (C=Ostr)

δ_H : see table 15, No.1

δ_C : see table 16, No.1

Found : C, 62.83; H, 7.59; N, 4.11%

$C_{17}H_{24}NO_3Cl$ requires : C, 62.67; H, 7.37; N, 4.30%

m/z : see table 17

3.3.14 Ethyl 8-(cyclopropylmethyl)-3α-(3-methoxyphenyl)-8-azabicyclo[3,2,1]octane-3β-carboxylate

(Ethyl N-(cyclopropylmethyl)-3α-(3-methoxyphenyl)-3β-nortropane carboxylate; 110)

Cyclopropylmethyl bromide (1.8g) was added dropwise to a mixture of ethyl 3α-(3-methoxyphenyl)-8-azabicyclo[3,2,1] octane-3β-carboxylate (108; 1.5g) and potassium carbonate (2.9g) in absolute ethanol (90ml). The resulting mixture was refluxed for 2 days, cooled and ether added (200ml). Solid material was filtered off and the filtrate washed with water (2 x 20ml), dried ($MgSO_4$) and evaporated in vacuo to give ethyl 8-(cyclopropylmethyl)-3α-(3-methoxyphenyl)-8-azabicyclo[3,2,1]octane-3β-carboxylate as a white solid. Treatment of an ethanolic solution of this solid with ethanolic-HCl gave the hydrochloride (1.1g; 56%), m.p. 184-185°C (acetone).

ν max : 1730cm^{-1} (C=Ostr)

δ_H : see table 15, No.2

δ_C : see table 16, No.2

Found : C, 66.73; H, 7.79; N, 3.73%

$C_{21}H_{30}NO_3Cl$ requires : C, 66.40; H, 7.91; N, 3.69%

m/z : see table 17

3.3.15 Ethyl 8-(cyclopropylmethyl)-3α-(3-hydroxyphenyl)-8-azabicyclo[3,2,1]octane-3β-carboxylate (1.15)

Ethyl 8-(cyclopropylmethyl)-3α-(3-methoxyphenyl)-8-azabicyclo-[3,2,1]octane-3β-carboxylate (1.10; 0.8g) in dry chloroform (5ml) was treated with boron tribromide in dichloromethane (1.0M; 10ml) by the same procedure described in section 3.3.12, to give ethyl 8-(cyclopropylmethyl)-3α-(3-hydroxyphenyl)-8-azabicyclo[3,2,1]-octane-3β-carboxylate as an oil. Treatment of this oil with ethereal-HCl gave the hydrochloride (66mg; 7.7%), m.p. 238°C (ethanol).

ν max : 3150-3250 cm^{-1} (O-H str), 1740 cm^{-1} (C=Ostr)

δ_H : see table 15, No.3

δ_C : see table 16, No.3

Found : C, 66.10; H, 7.33; N, 3.79%

$C_{20}H_{28}NO_3Cl$ requires : C, 65.66; H, 7.66; N, 3.83%

$^m/_z$: see table 17

3.3.16 Ethyl 8-allyl-3α-(3-methoxyphenyl)-8-azabicyclo[3,2,1] octane-3β-carboxylate

(Ethyl N-allyl-3α-(3-methoxyphenyl)-3β-nortropane carboxylate; 1.13)

Ethyl 3α-(3-methoxyphenyl)-8-azabicyclo[3,2,1]octane-3β-carboxylate (1.08; 1.5g) and potassium carbonate (2.9g) in absolute ethanol (90ml) were treated with allyl bromide (1.3g) by the same procedure described in section 3.3.14. Ethyl 8-allyl-3α-(3-methoxyphenyl)-8-

azabicyclo[3,2,1]octane-3β-carboxylate was obtained as a clear oil. Treatment of the oil with ethereal-HCl gave the hydrochloride (0.7g; 37%), m.p. 175°C (acetone).

ν max : 1740 cm^{-1} (C=Ostr)

δ_H : see table 15, No.4

δ_C : see table 16, No.4

Found : C, 65.46; H, 7.52; N, 3.81%

$C_{20}H_{28}NO_3Cl$ requires : C, 65.66; H, 7.66; N, 3.83%

m/z : see table 17

3.3.17 Ethyl 8-allyl-3α-(3-hydroxyphenyl)-8-azabicyclo[3,2,1] octane-3β-carboxylate (116)

Ethyl 8-allyl-3α-(3-methoxyphenyl)-8-azabicyclo[3,2,1]octane-3β-carboxylate (113; 0.6g) in dry chloroform (5ml) was treated with boron tribromide in dichloromethane (1.0M; 10ml) by the same procedure described in section 3.3.12, to give ethyl 8-allyl-3α-(3-hydroxyphenyl)-8-azabicyclo[3,2,1]octane-3β-carboxylate as an oil. Treatment of this oil with ethereal-HCl gave the hydrochloride (52mg; 8%), m.p. 199-201°C (ethanol).

ν max : 3200-3100 cm^{-1} (OHstr), 1740 cm^{-1} (C=Ostr)

δ_H : see table 15, No.5

δ_C : see table 16, No.5

Found : C, 64.59; H, 7.21; N, 3.79%

$C_{19}H_{26}NO_3Cl$ requires : C, 64.86; H, 7.39; N, 3.98%

m/z : see table 17

3.3.18 Ethyl 3α-(3-methoxyphenyl)-8-phenethyl-8-azabicyclo-[3,2,1]octane-3β-carboxylate

(Ethyl 3α-(3-methoxyphenyl)-N-phenethyl-3β-nortropane carboxylate; 109)

Ethyl 3α-(3-methoxyphenyl)-8-azabicyclo[3,2,1]octane-3β-carboxylate (108; 1.5g) and potassium carbonate (2.9g) in absolute ethanol (90ml) were treated with phenethyl bromide (1.4g) by the same procedure described in section 3.3.14. Ethyl 3α-(3-methoxyphenyl)-8-phenethyl-8-azabicyclo[3,2,1]octane-3β-carboxylate was obtained as an oil. Treatment of this oil with ethereal-HCl gave the hydrochloride (1.2g; 54%), m.p. 194°C (acetone).

ν max : 1730 cm^{-1} (C=Ostr)

δ_H : see table 15, No.6

δ_C : see table 16, No.6

Found : C, 70.00; H, 7.33; N, 3.03%

$C_{25}H_{32}NO_3Cl$ requires : C, 69.84; H, 7.45; N, 3.26%

m/z : see table 17

3.3.19 Ethyl 3α-(3-hydroxyphenyl)-8-phenethyl-8-azabicyclo-[3,2,1]octane-3β-carboxylate (114)

Ethyl 3α-(3-methoxyphenyl)-8-phenethyl-8-azabicyclo[3,2,1]octane-3β-carboxylate (109; 0.6g) in dry chloroform (10ml) was treated with boron tribromide (1.0M; 10ml) by the same procedure described in section 3.3.12, to give ethyl 3α-(3-hydroxyphenyl)-8-phenethyl-8-azabicyclo[3,2,1]octane-3β-carboxylate as a light brown semi-solid. Treatment of this semi-solid with ethereal-HCl gave the hydrochloride (113mg; 17%), m.p. 214-215°C (ethanol).

ν max : 3200-3450 cm^{-1} (OHstr), 1740 cm^{-1} (C=Ostr)

δ_H : see table 15, No.7

δ_C : see table 16, No.7

Found : C, 69.02; H, 6.99; N, 3.48%

$C_{24}H_{30}NO_3Cl$ requires : C, 69.31; H, 7.22; N, 3.37%

$^m/_z$: see table 17

3.3.20 Ethyl 8-(2-benzoylethyl)-3α-(3-methoxyphenyl)-8-azabicyclo[3,2,1]octane-3β-carboxylate

(Ethyl N-(2-benzoylethyl)-3α-(3-methoxyphenyl)-3β-nortropane carboxylate; 117)

Ethyl 3α-(3-methoxyphenyl)-8-azabicyclo[3,2,1]octane-3β-carboxylate (108; 0.8g) was dissolved in dry toluene (6ml) and phenyl vinyl ketone (1.5g) added. The solution was refluxed overnight and then evaporated in vacuo. The oily residue was dissolved in ether (100ml) and extracted with HCl (0.2M; 2 x 50ml). The aqueous

layer was washed with ether (3 x 60ml), basified with K_2CO_3 (30%; 60ml), and extracted with chloroform (3 x 100ml). The combined chloroform layer was washed with water (2 x 50ml), dried ($MgSO_4$) and evaporated *in vacuo* to give ethyl 8-(2-benzoylethyl)-3α-(3-methoxyphenyl)-8-azabicyclo[3,2,1]octane-3β-carboxylate as an oil. This oil was dissolved in acetone and treated with a solution of maleic acid in acetone to yield the *maleate salt* (1.3g; 87%), m.p. 145°C (acetone).

ν max : 1700, 1730 cm^{-1} (2 x C=Ostr)

δ_H : see table 15, No.8

δ_C : see table 16, No.8

Found : C, 67.20; H, 6.53; N, 2.46%

$C_{30}H_{35}NO_8$ requires : C, 67.04; H, 6.52; N, 2.60%

m/z : see table 17

Table 15 ^{1}H-N.M.R. CHARACTERISTICS OF SOME 3,3-DISUBSTITUTED NORTROPANES[a]

No.	Compound	N-CH_2	1(5)H[b]	2(4)H	6(7)H	Other Protons
1	108 HCl in $CDCl_3$ [n]		δ4.21, $W_{½}$ 11.5	β: δ2.82, ^2J17, ^3J3[c] α: δ2.96, ^2J17[c]	δ1.59[d], 1.96[e]	N-H δ9.66, broad s OCH_2 δ3.97, q, ^3J7 OCH_3 δ3.82, s CH_2CH_3 δ1.07, t, ^3J7 [e] Aryl-H δ6.84, 7.22
2	110 HCl in D_2O [n]	δ2.85,[d] ^3J7	δ4.19, $W_{½}$ 11	β: δ2.58, ^2J17[c] α: δ3.13 ^2J17[c]	δ1.61[d], 1.83[e]	OCH_2 δ3.97, q, ^3J7 OCH_3 δ3.81, s CH_2CH_3 δ1.00, t, ^3J7 N-CH_2CH g CH_2 / CH_2 δ 0.33, 0.68, d, ^3J7 Aryl-H δ6.99, 7.36[f]
3	115 HCl in D_2O	δ2.90,[d] ^3J7	δ4.23, $W_{½}$ 10	β: δ2.60 ^2J15, ^3J3[c] α: δ3.14 ^2J15[c]	δ1.66[d], 1.86[e]	OCH_2 δ4.00, q, ^3J7 CH_2CH_3 δ1.06, t, ^3J7 N-CH_2CH g CH_2 / CH_2 δ0.36, 0.72, d, ^3J7 Aryl-H δ6.90, 7.32[f]
4	113 in $CDCl_3$	δ2.87,[d] ^3J7	δ3.29, $W_{½}$ 13	δ3.15-3.23,[i]	δ1.68[d], 1.90[e]	OCH_2 δ4.06, q, ^3J7 OCH_3 δ3.80, s CH_2CH_3 δ1.19, t, ^3J7 $CH=CH_2$ δ5.82[j] $CH=CH_2$ δ5.14[k] Aryl-H δ6.73, 7.01, 7.20[l]
5	116 HCl in D_2O	δ3.61,[d] ^3J7	δ4.10, $W_{½}$ 11	β: δ2.57 ^2J16 α: δ3.18 ^2J16	δ1.67[d], 1.91[e]	OCH_2 δ4.02, q, ^3J7 CH_2CH_3 δ1.06, t, ^3J7 $CH=CH_2$ δ5.90, [j] $CH=CH_2$ δ5.53, [k] Aryl-H δ6.90, 7.20, 7.33, [m]
6	109 HCl in D_2O [n]	n	δ4.07, $W_{½}$ 10	β: δ2.57 ^2J16 n α:	δ1.59[d], 1.86[e]	OCH_2 δ3.97, q, ^3J7 OCH_3 δ3.80, s CH_2CH_3 δ1.01, t, ^3J7 CH_2Ph n Aryl-H 6.89, 7.32[o]
7	114 HCl in D_2O	n	δ4.11, $W_{½}$ 12	β: δ2.59 ^2J17 n α:	δ1.65[d], 1.90[e]	OCH_2 δ3.97, q, ^3J7 CH_2CH_3, δ1.05, t, ^3J7 CH_2Ph n Aryl-H δ6.89, 7.35[o]
8	117 in $CDCl_3$	δ3.13,t ^3J7	δ3.35, $W_{½}$ 16	β: δ3.20[p] α: δ2.11[q]	δ1.43[d], 1.63	OCH_2 δ4.01, q, ^3J7 OCH_3 δ3.74, s CH_2CH_3 δ1.12, t, ^3J7 O ‖ CH_2-C δ2.72, t, ^3J7 Aryl-H δ6.98-7.98[r]

Notes to Table 15

a. δ values refer to centres of resonance signals and hence represent only approximate chemical shifts in most cases. J (approx) and $W_{\frac{1}{2}}$ values are given in Hz.

b. Unresolved near-symmetrical multiplet.

c. 2-Proton signal with two prominent lines.

d. 2-Proton multiplet with two prominent lines.

e. 2-Proton multiplet.

f. Multiplets, higher 1 and lower field 2 proton intensity.

g. Signal overlaps CH_2-$\underline{CH_3}$ resonance.

h. Spectrum recorded on a JEOL GX 400 MHz FT NMR Spectrometer.

i. 4-Proton multiplet poorly resolved.

j. 1-Proton multiplet.

k. 2-Proton multiplet.

l. Multiplets, higher 1, middle 2 and lower field 1 proton intensity.

m. Multiplets, higher 1, middle 1 and lower field 2 proton intensity.

n. Signals overlap.

o. Multiplets, higher 1 and lower field 8 proton intensity.

p. Broad multiplet.

q. Narrow multiplet.

r. Complex multiplet of 9 proton intensity.

Table 16 ^{13}C-NMR CHEMICAL SHIFTS OF SOME 3,3' DISUBSTITUTED NORTROPANES

^{13}C Chemical Shifts (p.p.m.; TMS Internal Standard)

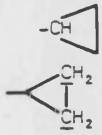
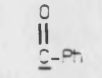
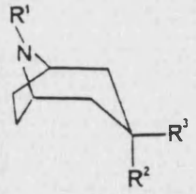
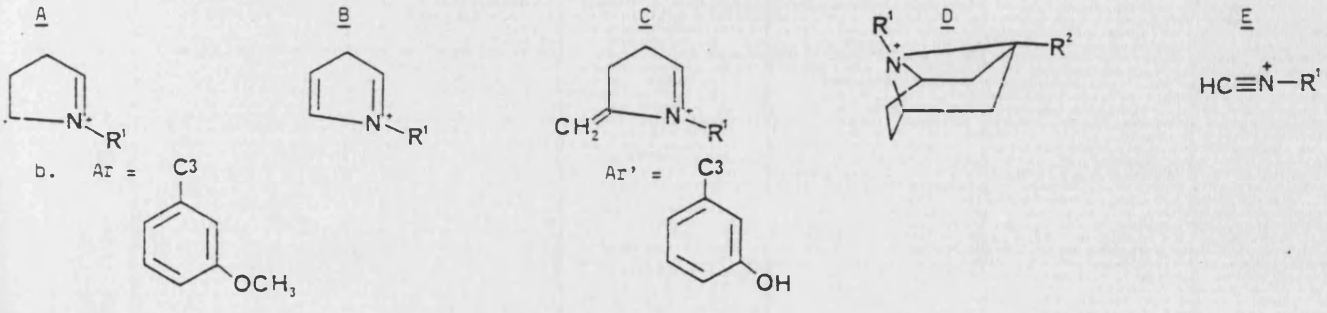
	No.	1	2	3	4	5	6	7	8
	Compound	108	110	115 HCl	113	116 HCl	109 HCl	114 HCl	117
	Solvent	$CDCl_3$	$CDCl_3$	D_2O	$CDCl_3$	D_2O	D_2O	D_2O	$CDCl_3$
	N-CH_2		55.66	55.45	55.12	53.09	51.96	51.96	47.11
	C-1 -5	52.94	58.09	60.91	56.45	60.64	61.69	61.71	57.39
	C-2 -4	40.04	39.20	34.09	41.79	34.20	34.09	34.07	41.77
	C-6 -7	31.15	26.31	22.28	28.75	22.15	22.25	22.22	29.01
	C-3	46.04	45.60	45.29	45.97	45.31	45.25	45.13	45.99
	C=O	175.9	174.4	176.1	175.3	176.0	176.0	174.5	175.2
	O-CH_3	55.14	55.22		55.22		55.46		55.01
Aromatic C	C-1'	143.7	141.8	140.0	144.2	139.9	139.8	139.1	144.1
	C-2'	111.4	111.7	114.3	111.4	114.3	113.0	114.2	111.5
	C-3'	159.2	159.4	155.8	159.3	155.8	159.1	155.8	159.4
	C-4'	113.4	113.4	114.9	113.1	114.9	113.6	114.9	113.1
	C-5'	128.9	129.2	130.0	129.0	126.2	129.9	130.0	133.0
	C-6'	119.2	119.1	119.2	119.0	119.2	119.8	119.2	118.9
Ester	CH_2	60.67	60.95	62.85	60.46	62.88	62.86	62.88	60.38
	CH_3	13.92	13.98	12.81	14.11	12.81	12.81	12.81	14.12
Nitrogen Substituent			8.30	5.66					
			3.76	3.18					
	CH=CH_2				136.4	130.0			
	CH=CH_2				116.4	125.8			
	N-CH_2CH_2						30.55	36.55	38.27
	Cq						136.5	136.5	136.9
	Co						129.1	129.1	129.0
	Cm						128.8	128.8	128.6
	Cp						127.4	127.4	128.0
									199.1

Table 17 PERCENT ABUNDANCE OF DIAGNOSTIC FRAGMENT IONS OF SOME 3,3-DISUBSTITUTED TROPANES AND RELATED COMPOUNDS



					ION TYPES [a]					
Compound	R^1	R^2 [b]	R^3	M^+	A	B	C	D	E	Other
90	Me	CO_2Me	OH	23	27	100	28	8	39	M^+-R^2(53)
96	Me	Ar-C(OH)-Ar	OH	42	36	30	8	18	-	M^+-R^2 (100); R^{2+} (50)
99	Me	Ar	Ar-C(=O)-	13	58	48	-	100	18	R^{3+} (18)
101	Me	Ar	Ar-C(=N-OH)-	11	100	45	-	11	13	
103	Me	Ar	COOH	40	100	92	47	50	53	
105	Me	Ar	CO_2Et	45	100	92	47	42	28	
70	Me	Ar'	CO_2Et	42	92	100	45	52	33	
108	H	Ar	CO_2Et	19	100	30	21	12	-	
110	CH_2-cyclopropyl	Ar	CO_2Et	19	35	100	25	24	-	R^{1+} (51)
115	CH_2-cyclopropyl	Ar'	CO_2Et	15	39	100	20	23	-	R^{1+} (44)
113	CH_2-CH=CH_2	Ar	CO_2Et	50	49	100	47	35	-	R^{1+} (35)
116	CH_2-CH=CH_2	Ar'	CO_2Et	45	53	100	45	45	27	R^{1+} (56)
109	$PhCH_2CH_2$	Ar	CO_2Et	0.6	-	2	-	2.5	-	R^{1+} (13); M^+-91 (100)
114	$PhCH_2CH_2$	Ar'	CO_2Et	c	13	7	5	-	-	M^+-91 (93)
117	$PhCCH_2CH_2$ (=O)	Ar	CO_2Et	25	20	23	13	22	-	$PhCOCH=CH_2^+$ (27); $PhCO^+$ (68)

a. Ion types are:



b. Ar =

Ar' =

c. M^+ not seen; M+1 observed in ISO-BUT CI spectrum (380; 32%).

3.3.21 3α-Hydroxy-8-methyl-3β-phenyl-8-azabicyclo[3,2,1]octane

(3β-Phenyl-3α-tropanol; 129; R=H)

Tropan-3-one (10g) in dry ether (50ml) was added to a stirred solution of phenyl-lithium {prepared from bromobenzene (46g) and lithium (2.2g)} in dry ether (100ml) over a period of 20 minutes. The mixture was stirred for 30 minutes at room temperature and then refluxed for 90 minutes. The resulting solution was cooled, poured onto ice and HCl (2M; 50ml) and a solid separated. This solid was washed with ether (2 x 50ml), basified with NaOH (20%) and the liberated free base extracted with chloroform (3 x 100ml). The combined chloroform extracts were washed with water (2 x 50ml), dried ($MgSO_4$) and evaporated to yield 3α-hydroxy-8-methyl-3β-phenyl-8-azabicyclo[3,2,1]octane as a white solid (7.9g; 51%), m.p. 159-160°C (Lit.,[121] 161-162.5°C).

ν max : 3200-3400 cm^{-1} (OH str)

δ_H : see table 18, No.1

δ_C : see table 19, No.1

m/z : see table 20

3.3.22 3α-Acetyloxy-8-methyl-3β-phenyl-8-azabicyclo[3,2,1] octane

(59)

Tropan-3-one (10g) in dry ether (50ml) was added to a stirred solution of phenyl-lithium {prepared from bromobenzene (46g) and lithium (2.2g)} in dry ether (100ml). The mixture was stirred overnight and then refluxed for 1 hour. The resulting solution was cooled and acetic anhydride added (50ml). The mixture was stirred for 5 hours and then poured onto ice and acetic acid (50ml). The

aqueous layer was separated, washed with ether (2 x 100ml), basified with K_2CO_3 and extracted with chloroform (3 x 100ml). The combined chloroform extracts were washed with water (2 x 50ml), dried ($MgSO_4$) and evaporated *in vacuo* to yield a dark brown oil. The oil was triturated with petroleum spirit (b.p. 60-80°C) and the petroleum spirit was separated and evaporated *in vacuo* to yield a yellow oil. Treatment of this oil with ethereal-HCl and subsequent recrystallisation from ethanol gave 3α-acetyloxy-8-methyl-3β-phenyl-8-azabicyclo[3,2,1]octane hydrochloride (9.3g; 44%) m.p. 198°C.

ν max : 1750 cm^{-1} (C=Ostr)

δ_H : see table 18, No.2

δ_C : see table 19, No.2

m/z : see table 20

3.3.23 8-Methyl-3-phenyl-8-azabicyclo[3,2,1]oct-2-ene

(3-Phenyltrop-2-ene; 130; R=H)

A mixture of 3α-hydroxy-8-methyl-3β-phenyl-8-azabicyclo[3,2,1]octane (129; R=H; 6g), concentrated HCl (46ml) and glacial acetic acid (96ml) was heated under reflux for 12 hours. Most of the solvent was removed *in vacuo*, the residue dissolved in water and the solution made alkaline with NH_4OH. This was extracted with chloroform (3 x 75ml). The combined chloroform extract was dried ($MgSO_4$) and evaporated to give 8-methyl-3-phenyl-8-azabicyclo[3,2,1]oct-2-ene as an oil which was distilled, and the fraction having b.p. 126°C/1.5mm Hg collected (5.2g; 95%)

(Lit.,[121] b.p. for 130; R=H, 113-115°C/0.45 mm Hg).

ν max : 1600, 1500cm^{-1} (C=Cstr)

δ_H : see table 18, No.3

δ_C : see table 19, No. 3

m/z : see table 20

3.3.24 8-Methyl-3α-phenyl-8-azabicyclo[3,2,1]octane

(3α-Phenyltropane; 131; R=H)

8-Methyl-3-phenyl-8-azabicyclo[3,2,1]oct-2-ene (130; R=H; 3g) in methanol (100ml) was hydrogenated over palladium charcoal (0.5g) at 60 p.s.i. in a rocking Parr apparatus at room temperature for 16 hours. The catalyst was filtered off and the filtrate evaporated to give 8-methyl-3α-phenyl-8-azabicyclo[3,2,1]octane as an oil. Treatment of this oil with ethereal-HCl gave the hydrochloride (2.1g; 58%), m.p. 218-219°C (Lit.,[163] m.p. 217.4-218.8°C).

ν max : 770, 720 cm^{-1} (monosub. benzene)

δ_H : see table 18, No.4

δ_C : see table 19, No.4

m/z : see table 20

3.3.25 8-Methyl-3β-phenyl-8-azabicyclo[3,2,1]octane

(3β-Phenyltropane; 132)

3α-Hydroxy-8-methyl-3β-phenyl-8-azabicyclo[3,2,1]octane (129; R=H; 3g) was added rapidly to a stirred suspension of Raney Ni (30g) in absolute ethanol (300ml), and refluxed for 48 hours. The catalyst was filtered off and the ethanol removed in vacuo to yield a white

semi-solid. Ether (100ml) was added to this semi-solid, the solid material which formed was filtered off (shown to be 129; R=H). The filtrate was dried ($MgSO_4$) and evaporated *in vacuo* to yield an oil which was distilled. The fraction having b.p. 110°C/4mm Hg was collected (0.2g; 7%) (Lit.,[163] b.p. for 132, 92-94°C/0.2mm Hg). Treatment of the oil with ethereal-HCl gave 8-methyl-3β-phenyl-8-azabicyclo[3,2,1]octane hydrochloride, m.p. 205°C (Lit.,[163] m.p. 203.2 - 205.2°C).

ν max : 760, 710 cm^{-1} (monosub. benzene)

δ_H : see table 18, No.5

δ_C : see table 19, No.5

$^m/_z$: see table 20

3.3.26 3α-Hydroxy-3β-(3-methoxyphenyl)-8-methyl-8-azabicyclo-[3,2,1]octane (125)

n-Butyl lithium (7.7g) in hexane was added to 3-bromoanisole (22.4g) in anhydrous tetrahydrofuran (100ml) under N_2 at -55°C. The mixture was stirred at -50°C for 2 hours and then tropan-3-one (10g) was added, with stirring at -45°C, over 30 minutes. The mixture was stirred at 25°C for 1 hour, cooled to -10°C and then quenched with iced-water. Following acidification with HCl (6M) the mixture was extracted with ether (3 x 100ml). The aqueous layer was basified with aqueous NaOH (5M) and the product extracted with ether (3 x 100ml). The ether extract was washed with water (2 x 25ml), dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil. Anhydrous ether (50ml) was added to this oil and 3α-hydroxy-3β-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]

octane separated as a white solid (5.4g; 30%), m.p. 125-126°C (ethylacetate).

ν max : 3100-3300 cm^{-1} (OHstr)

δ_H : see table 18, No.6

δ_C : see table 19, No.6

Found: C, 72.77; H, 8.74; N, 5.49%

$C_{15}H_{21}NO_2$ requires : C, 72.87; H, 8.50; N, 5.66%

m/z : see table 20

3.3.27 3-(3-Methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]oct-2-ene (130; R=OMe)

3α-Hydroxy-3β-(3-methoxyphenyl)-8-methyl-8-azabicyclo[3,2,1]-octane (125; 2g) was treated with concentrated HCl (40ml) and glacial acetic acid (80ml) by the same procedure as described in section 3.3.23 to give 3-(3-methoxyphenyl)-8-methyl-8-azabicyclo-[3,2,1] oct-2-ene as a clear oil (1.4g; 76%). Treatment of this oil with ethereal-HCl gave the hydrochloride, m.p. 220°C (acetone).

ν max : 770, 720 cm^{-1} (monosub. benzene)

δ_H : see table 18, No.7

δ_C : see table 19, No.7

Found: C, 67.87; H, 7.84; N, 5.04%

$C_{15}H_{20}NOCl$ requires : C, 67.79; H, 7.53; N, 5.27%

m/z : see table 20

3.3.28 3α-Hydroxy-3β-(3-hydroxyphenyl)-8-methyl-8-azabicyclo-[3,2,1]octane (129; R=OH)

n-Butyl lithium (1.3g) in hexane was added to 3-(2-tetrahydropyranyloxy)bromobenzene (4.5g) in anhydrous tetrahydrofuran (50ml) under N_2 at -55°C over a period of 20 minutes. The mixture was stirred at -50°C for 2 hours and then tropan-3-one (2g) in tetrahydrofuran (30ml) was added, with stirring at -45°C, over 30 minutes. The mixture was then poured onto ice and ammonium chloride and extracted with ether (3 x 100ml). The combined ether extracts were washed with water (2 x 25ml), dried ($MgSO_4$) and then evaporated in vacuo to yield a light yellow oil. Treatment of this oil with ethereal-HCl yielded 3α-hydroxy-3β-(3-hydroxyphenyl)-8-methyl-8-azabicyclo[3,2,1]octane hydrochloride as a white solid (2.3g; 59%), m.p. 254°C (ethanol).

ν max : 3200-3400 cm^{-1} (OHstr)

δ_H : see table 18, No.8

δ_C : see table 19, No.8

Found: C, 62.48; H, 7.49; N, 5.12%

$C_{14}H_{20}NO_2Cl$ requires : C, 62.33; H, 7.42; N, 5.19%

m/z : see table 20

Table 18 ^{1}H-N.M.R. CHARACTERISTICS OF SOME 3,3-DISUBSTITUTED TROPANES[a]

No.	Compound	N-CH_3	1(5)-H	2(4)-H	6(7)-H	Other Protons
1	(129; R=H) in $CDCl_3$ [b]	δ2.33, s	δ3.23 d $W_{½}$ 10	δ2.26 [e] δ2.02 [f]	δ1.76 ^2J14 δ2.40 ^2J14 ^3J3	OH δ1.70 broad s Aryl-H δ7.25, 7.52
2	(59) in $CDCl_3$ [c]	δ2.3, s	δ3.25 d $W_{½}$ 8	g	g	$COCH_3$ δ1.98, s Aryl-H δ7.20, s
3	(130; R=H) in $CDCl_3$	δ2.37, s	δ3.38 [h]	i	i	CH=C δ6.22, d, J6.5 Aryl-H δ7.15-7.37, m
4	(131; R=H) HCl in $CDCl_3$ [b]	δ2.74, s	δ3.81 d $W_{½}$ 10	δ3.15 [f] δ2.56 [e]	δ1.84 δ2.00	3-H δ3.44, broad t $^3J \sim 7$ Aryl-H δ7.24-7.44, m
5	(132) in $CDCl_3$	δ2.30. s	δ3.22 d $W_{½}$ 9	δ2.05 δ1.90	δ1.65 [j]	3-H δ2.83, septet Aryl-H δ7.15-7.29, m
6	(125; R=OMe) in $CDCl_3$ [b]	δ2.32, s	δ3.21 d $W_{½}$ 9	δ2.34 [e] δ2.02 [f]	δ1.78, ^2J14 δ2.39, ^2J14 ^3J3	OCH_3 δ3.79, s Aryl-H δ6.75, 7.08, 7.23
7	(129; R=OH) in $CDCl_3$	δ2.39, s	δ3.40 [h]	i	i	OCH_3 δ3.84, s CH=C δ6.25 J6.5 Aryl-H δ7.18-7.39, m
8	(129, R=OH) HCl in D_2O [b]	δ2.77, s	δ3.92, d $W_{½}$ 11	[k] δ2.24 [f]	δ2.08, ^2J17 [k]	Aryl-H δ6.77, 6.96 7.25

a. δ values refer to centres of resonance signals and hence represent only approximate chemical shifts in most cases.
J (approx) and $W_{½}$ values are given in Hz.

b. Spectra recorded on a JEOL GX 400MHz FT N.M.R. Spectrometer.

c. Spectrum recorded on a JEOL JNM-PMX 60MHz NMR Spectrometer.

d. Unresolved near symmetrical multiplet.

e. 2-Proton multiplet with two prominent lines.

f. 2-Proton multiplet.

g. Overlapping unresolved multiplets (δ2.0-δ2.5).

h. 2-Proton complex multiplet.

i. Multiplets (δ1.51-2.22; 6H) and (δ2.74-2.90; 2H).

j. Part of two overlapping multiplets (4-proton intensity).

k. Two 2-proton multiplets which overlap.

Table 19 ^{13}C-N.M.R. CHARACTERISTICS OF SOME 3,3-DISUBSTITUTED TROPANES AND RELATED COMPOUNDS[a]

		^{13}C Chemical Shifts (ppm; TMS Int. Standard)											
No.	Compound	N-CH_3	C-1 -5	C-2 -4	C-6 -7	C-3	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	Other Carbons
1	129; R=H	40.29	60.79	45.43	25.53	72.64	150.3	128.0	124.5	126.5	124.5	128.0	
2	59 [b]	39.76	60.46	40.47	25.46	78.66	145.5	128.1	124.2	126.8	124.2	128.1	169.3 [c] 22.54
3	130; R=H [b]	34.83	(57.75) (56.12)	125.4 32.13	(31.37) (28.33)	130.8	138.6	126.7	123.1	125.5	123.1	126.7	
4	131; R=H	40.63	59.71	38.55	27.99	32.34	146.3	128.1	127.2	125.5	127.2	128.1	
5	132	40.54	61.59	39.23	26.22	34.87	145.9	128.4	127.2	126.0	127.2	128.4	
6	125	40.32	60.78	45.37	25.62	72.88	152.2	110.6	159.5	111.8	129.1	117.0	55.27 [d]
7	130; R=OMe [b]	36.24	(59.37) (57.75)	124.2 33.80	(32.99) (32.99)	132.5	141.8	110.9	159.8	112.3	127.1	117.3	54.98 [d]
8	129;R=OH	40.03	61.07	44.83	25.11	77.33	151.5	113.7	157.4	114.8	129.1	115.5	

a. Bases in $CDCl_3$; values in parentheses may be interchanged.

b. Spectra were recorded on JEOL FX90X Fourier Transform NMR Spectrometer operating at 22.5 MHz.

c. High field resonance (CH_3); low field resonance (C=O).

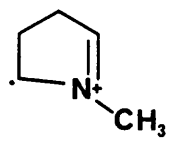
d. OMe signal of aryl group.

Table 20 PERCENT ABUNDANCE OF DIAGNOSTIC FRAGMENT IONS OF SOME 3,3-DISUBSTITUTED TROPANES AND RELATED COMPOUNDS

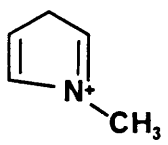
			ION TYPES[a]					
No.	Compound	$M^{+\cdot}$	A	B	C	D	E	F
1	129; R=H	23	100	75	43	13	-	42
2	59	b	-	-	-	4	63	13
3	130; R=H	13	-	-	-	-	100	5
4	131; R=H	38	100	100	43	-	17	47
5	132	43	100	97	43	-	32	52
6	125	30	100	72	55	12	-	30
7	130; R=OMe	c	-	-	-	-	5	13
8	129; R=OH	33	100	75	50	12	-	28

a. Ion types are:

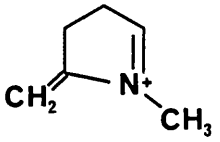
A



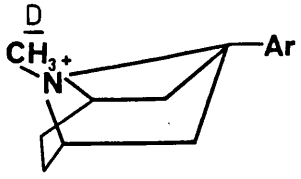
B



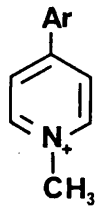
C



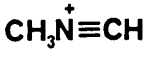
D



E



F



b. $M^{+\cdot}$ not seen; M+1 observed in ISO-BUT CI spectrum (260; 3%)

c. $M^{+\cdot}$ not seen;

3.4 The Piperidines

3.4.1 Diethyl 3,4-dimethyl-4-azaheptanedioate (141)

Ethyl crotonate (120g) was added to 33% w/v methylamine in I.M.S. (100ml); the mixture was heated under reflux for 8 hours and then fractionated to give ethyl 3-methylaminobutyrate b.p. 68°C/10mm Hg (85g; 56%). (Lit.,[188] b.p. 72°C/12.5mm Hg).

ν max : 1730cm^{-1} (C=Ostr)

δ_H ($CDCl_3$; free base):

1.21 (3H; t; CH_2-$\underline{CH_3}$), 1.36 (3H; d; CH-$\underline{CH_3}$), 2.29 (2H; d; CH-$\underline{CH_2}$-CO), 2.50 (3H; s; $\underline{N}$-$\underline{CH_3}$), 2.95 (1H; m; $\underline{CH}$-CH_3), 4.16 (2H; q; -O-$\underline{CH_2}CH_3$).

δ_C ($CDCl_3$; free base):

14.35 (CH_2-$\underline{CH_3}$), 20.15 (CH-$\underline{CH_3}$), 33.75 ($\underline{N}$-$\underline{CH_3}$), 41.50 (CH-$\underline{CH_2}$-CO), 52.28 ($\underline{CH}$-CH_3), 60.03 (O-$\underline{CH_2}$-CH_3), 172.0 ($\underline{C}$=O)

A mixture of ethyl 3-methylaminobutyrate (80g) and ethyl acrylate (65g) was kept at room temperature for 10 days and then fractionated to give diethyl 3,4-dimethyl-4-azaheptanedioate, b.p. 108°C/1mm Hg (84g; 62%) (Lit.,[189] b.p. 129°C/6mm Hg).

ν max : 1730cm^{-1}, 1750cm^{-1} (C=str).

δ_H ($CDCl_3$; free base):

1.20 (3H; d; CH-$\underline{CH_3}$), 1.43 (6H; t; 2 x CH_2-$\underline{CH_3}$), 2.33 (3H; s; $\underline{N}$-$\underline{CH_3}$), 2.49-2.83 (6H; m; 2 x $\underline{CH_2}$-CO, $\underline{CH_2}$-$\underline{N}$), 3.33 (1H; m; $\underline{CH}$-CH_3), 4.20 (4H; q; 2 x O-$\underline{CH_2}$-CH_3).

δ_C ($CDCl_3$; free base) :

13.81 (2 x $CH_2\underline{C}H_3$), 33.48 ($CH_2\underline{C}H_2CO$), 35.97 ($\underline{N}$-$\underline{C}H_3$), 38.19 (CH-$\underline{C}H_2CO$), 48.65 ($CH_2\underline{C}H_2\underline{N}$), 55.37 ($\underline{C}$H-$CH_3$), 59.59 (2 x O-$\underline{CH_2}$-$CH_3$), 171.62 (2 x $\underline{C}$=O)

3.4.2 1,2-Dimethyl-4-piperidone (138)

Diethyl 3,4-dimethyl-4-azaheptanedioate (141; 50g) was added slowly to a stirred mixture of sodium amide (11g) in toluene (400ml). The product was heated under reflux overnight, then cooled and acidified cautiously with hydrochloric acid (2M). The toluene layer was separated and extracted with dilute HCl (5 x 100ml), and the combined acids were then heated under reflux for 15 hours. The solution was concentrated under reduced pressure, basified with solid NaOH and extracted with chloroform (8 x 150ml). The combined chloroform extracts were washed with water (2 x 100ml), dried ($MgSO_4$) and evaporated <u>in vacuo</u>. The residue was fractionated to give 1,2-dimethyl-4-piperidone, b.p. 36-40°C/0.2mm Hg (13.5g; 51%) (Lit.,[75] 55-57°C/7mm Hg).

ν max : 1730cm^{-1} (C=Ostr)

δ_H ($CDCl_3$; free base):

1.20 (3H; d; CH-$\underline{C}H_3$), 2.43 (3H; s; $\underline{N}$-$\underline{C}H_3$), 2.20-2.90 (6H; m; C3-$\underline{H}$, C5-$\underline{H}$, C6-$\underline{H}$), 3.00-3.33 (1H; m; C2-$\underline{H}$).

δ_C ($CDCl_3$; free base):

19.61 (C2-$\underline{C}H_3$), 41.12 (C-5), 41.44 ($\underline{N}$-$\underline{C}H_3$), 48.59 (C-3), 54.55 (C-6), 58.51 (C-2), 207.16 ($\underline{C}$=O)

3.4.3 α- and β- 1,2-Dimethyl-4-phenylpiperidin-4-ol (139 and 140)

1,2-Dimethyl-4-piperidone (138; 15g) was added to phenyl-lithium {from bromobenzene (23g) and lithium (2.0g)} in dry ether (150ml). The mixture was stirred overnight at room temperature and then refluxed for 4 hours. The cooled product was poured onto ice and acetic acid (40ml). The aqueous phase was separated, washed with ether (2 x 40ml), and concentrated under reduced pressure. It was then made alkaline with strong aqueous ammonia and the liberated free base extracted with chloroform (6 x 100ml). The combined chloroform extract was dried ($MgSO_4$) and evaporated to yield a light yellow oil. This residue was diluted with petroleum spirit (b.p. 60-80°C; 750ml) and the resultant solid was recrystallised from the same solvent to give β-1,2-dimethyl-4-phenylpiperidin-4-ol (10.4g; 43%), m.p. 108-110°C. (Lit.,[75] 106-108°C).

ν max : 3050-3300cm^{-1} (O-Hstr), 760, 710cm^{-1} (monosub. benzene).

δ_H : see table 21

δ_C : see table 22, No.2

m/z : M^+ (66%), 70 (100%), 71 (18%), 42 (23%)

The mother liquors were reduced in volume under reduced pressure to approximately 250ml and left to stand overnight. A solid was deposited which was shown to be α-1,2-dimethyl-4-phenylpiperidin-4-ol (9.8g; 40%), m.p. 120°C. (Lit.,[75] 122-123°C).

ν max : 3100-3400 cm^{-1} (OH str), 770, 710cm^{-1} (monosub. benzene).

δ_H : see table 21

δ_C : see table 22, No.1

m/z : $M^{\dot{+}}$ (73%), 70 (100%), 71 (25%), 42 (27%).

3.4.4 (±)-α-4-Acetyloxy-1,2-dimethyl-4-phenylpiperidine

Acetyl chloride (4.0g) was added to (±)-α-1,2-dimethyl-4-phenylpiperidin-4-ol(139; 1.0g) in toluene (130ml) and the mixture was heated under reflux overnight. The cooled product was diluted with ether and the (±)-α-4-acetyloxy-1,2-dimethyl-4-phenylpiperidine hydrochloride (0.61g; 44%), m.p. 186°C, (Lit.,[75] 184-185°C) collected by filtration.

ν max : 1750cm^{-1} (C=O str)

δ_H ($CDCl_3$; free base):
1.10 (3H; d, ^3J 6.2 Hz; C-2-CH_3), 1.69 (1H; d x d, ^2J 16 Hz, ^3J 11.3 Hz; ax 3-H), 2.03 (3H; s; $COCH_3$), 2.32 (3H; s; N-CH_3), 2.06-2.25 (5H; m; C-2-H, eq 3-H, eq 5-H, ax 5-H, ax 6-H), 2.78 (1H; d x q, ^2J 13.5 Hz, ^3J 6 Hz, 2.3 Hz; eq 6-H), 7.21-7.33 (5H; m; Ar-H).

δ_C : see table 22, No.3

m/z : $M^{\dot{+}}$ (8%), 187 (100%), 172 (75%).

Table 21 ^{1}H-N.M.R. CHARACTERISTICS OF α- AND β- 1,2-DIMETHYL-4-PHENYLPIPERIDIN-4-OL[a]

	No.1 α-1,2-Dimethyl-4-phenylpiperidin-4-ol	No.2 β-1,2-Dimethyl-4-phenylpiperidin-4-ol
N-CH_3	δ2.35, s	δ2.22, s
C2-CH_3	δ1.10, d J 6.25	δ1.13, d J 6.2
2-H	δ2.40, m [b]	~δ2.10, m [c]
ax 3H	d	δ1.77 ^{2}J13.6, ^{3}J10.5
eq 3H	d	e
ax 5H	δ2.20, ^{2}J13.6, ^{3}J13.6, 5.0	e
eq 5H	d	e
ax 6H	δ2.62 ^{2}J11.8, ^{3}J11.8, 2.48	e
eq 6H	δ2.80 ^{2}J11.8, ^{3}J4.3, 2.48	δ2.80 ^{2}J11.7, ^{3}J2.6, 2.6
Aryl-H	δ7.26, 7.35, 7.5 [f]	δ7.30, 7.40, 7.50 [f]

a. Spectra recorded in $CDCl_3$ with internal tetramethylsilane. δ values refer to centres of resonance signals and hence represent only approximate chemical shifts in most cases. J (approx) values are given in Hz.

b. Complex multiplet, signal reduces to doublet of doublets (^{3}J11.2, 3.1 Hz) by irradiation of C-2-methyl doublet.

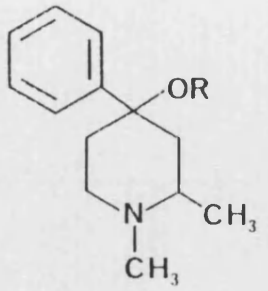
c. Part of multiplet at δ2.1; irradiation at δ2.1 causes the C-2-methyl doublet to reduce to a singlet.

d. Poorly resolved multiplet (δ1.70-1.84; proton intensity 3H).

e. Signals part of poorly resolved multiplets.

f. Multiplets, higher 1, middle 2 and lower field 2 proton intensity.

Table 22 ^{13}C- N.M.R. CHEMICAL SHIFTS OF 2-METHYL ANALOGUES OF REVERSED ESTERS OF PETHIDINE [a]



				^{13} Chemical Shifts (ppm; TMS Int. Standard)											
No.	Compound	Isomer Designation	R	N-CH_3	C-2	C-3	C-4	C-5	C-6	C-2 -Me	Aromatic C				
											Cq	Co	Cm	Cp	R
1	139	α-	H	42.13	56.26	44.13	71.65	38.26	53.06	19.62	145.0	128.3	126.6	127.3	
2	140	β-	H	42.73	54.62	47.22	71.87	38.27	52.53	20.30	148.6	128.2	124.5	126.9	
3	acetate ester of 139	α-	$COCH_3$	42.49	54.26	44.21	81.05	35.84	52.26	20.28	144.0	128.2	124.1	127.0	169.0 21.90

a. Spectra recorded as base in $CDCl_3$.

3.4.5 Resolution of (±)-α-1,2-dimethyl-4-phenylpiperidin-4-ol

A solution of (±)-α-1,2-dimethyl-4-phenylpiperidin-4-ol (1.39; 1.2g) in methanol (50ml) was added to a suspension of (-)-3'-nitrotartranilic acid (2.17g) in methanol (50ml), and the mixture heated on a steam bath for 5 minutes. The solution was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in a minimum amount of warm methanol and the solution allowed to cool to room temperature before refrigeration at -5°C overnight. A solid (wt. 1.9g) with $[\alpha]_D^{23}$ - 55.0° (C=0.5, MeOH) formed. After four additional crystallisations, 800mg of resolved material (no improvement of rotation on repeated recrystallisation) with m.p. 196°C and $[\alpha]_D^{23}$ -60.0° (C=0.5, MeOH) was obtained. The (+)-free base was generated by addition of NH_4OH to the salt and extraction with dichloromethane (3 x 50ml). The dichloromethane extracts were dried ($MgSO_4$), evaporated and the remaining solid recrystallised from petroleum spirit (b.p. 40-60°C) to give (+)-α-1,2-dimethyl-4-phenylpiperidin-4-ol, (0.22g) $[\alpha]_D^{23}$ + 1.0° (C=1.0, MeOH) m.p. 119°C.

Partially resolved (-)-α-1,2-dimethyl-4-phenylpiperidin-4-ol was recovered from the resolution mother liquors by addition of base (10% NaOH) and extraction with chloroform (3 x 30ml). Solvent was removed from the extract *in vacuo* to give crude (-)-α-1,2-dimethyl-4-phenylpiperidin-4-ol (0.8g). This base was combined with (+)-3'-nitrotartranilic acid (1.45g) and treated as described above to afford (-)-α-1,2-dimethyl-4-phenylpiperidin-4-ol-(+)-3'-nitrotartranilate m.p. 201°C $[\alpha]_D^{23}$ + 60.0° (C=0.5, MeOH). Isolation of the free base, as described for the antipode, gave

(-)-α-1,2-dimethyl-4-phenylpiperidin-4-ol (0.32g) $[\alpha]_D^{23}$ -1.0° (C=1.0,MeOH) m.p. 120°C.

{see table 23 for full range of optical rotation readings}

3.4.6(a) (+)-α-4-Acetyloxy-1,2-dimethyl-4-phenylpiperidine

The procedure described in section 3.4.4 was employed using (+)-α-1,2-dimethyl-4-phenylpiperidin-4-ol(0.2g) and acetyl chloride (0.8g). This gave (+)-α-4-acetyloxy-1,2-dimethyl-4-phenylpiperidine hydrochloride (0.13g; 46%) m.p. 196°C.

ν max : 1765cm^{-1} (C=O str), 770, 710cm^{-1} (monosub. benzene)

Found : C, 63.49; H, 7.88; N, 4.64%

$C_{15}H_{22}NO_2Cl$ requires: C, 63.49; H, 7.76; N, 4.94%

(b) (-)-α-4-Acetyloxy-1,2-dimethyl-4-phenylpiperidine

The procedure described in section 3.4.4 was employed using (-)-α-1,2-dimethyl-4-phenylpiperidin-4-ol (0.3g) and acetyl chloride (1.2g). This gave (-)-α-4-acetyloxy-1,2-dimethyl-4-phenylpiperidine hydrochloride (0.16g; 40%) m.p. 200°C.

ν max : 1765cm^{-1} (C=Ostr), 775 710cm^{-1} (monosub. benzene)

Found : C, 63.43; H, 7.94; N, 4.78%

$C_{15}H_{22}NO_2Cl$ requires: C, 63.49; H, 7.76; N, 4.94%

Table 23 SPECIFIC ROTATION ([α]) OF (+)-α-1,2-DIMETHYL-4-PHENYLPIPERIDIN-4-OL-(-)-3'-NITROTARTRANILATE AND (-)-α-1,2-DIMETHYL-4-PHENYLPIPERIDIN-4-OL-(+)-3'-NITROTARTRANILATE

Diastereoisomeric Salt [a]	Wavelength (nm)	$[\alpha]^{23}$
(+)-α-1,2-dimethyl-4-phenyl-piperidin-4-ol-(-)-3'-nitrotartranilate	589 578 546 436	-60^0 -64^0 -74^0 -118^0
(-)-α-1,2-dimethyl-4-phenyl-piperidin-4-ol-(+)-3'-nitrotartranilate	589 578 546 436	$+60^0$ $+64^0$ $+72^0$ $+120^0$

a. Concentration = 0.5% w/v, solvent = methanol.

3.4.7 4-(3-Methoxyphenyl)-1-methylpiperidin-4-ol (149)

N-Methylpiperidone (10g) was added to the Grignard reagent prepared from m-bromoanisole (28g) and magnesium (3.8g) in dry tetrahydrofuran (150ml). The solution was refluxed for 1 hour and then stirred overnight at room temperature. The cooled product was poured onto a mixture of crushed ice and acetic acid (50ml) and extracted with ether (2 x 50ml). The aqueous layer was basified with saturated K_2CO_3 solution and extracted with ether (3 x 100ml). The combined ether layer was washed with water (2 x 30ml), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. This oil was diluted with petroleum spirit (b.p. 30-40°C; 100ml) and the resultant solid recrystallised from the same solvent to give 4-(3-methoxyphenyl)-1-methylpiperidin-4-ol as a white solid (6.1g; 31%), m.p. 110°C (Lit.,[56] 112-113°C).

ν max : 3300-3100cm^{-1} (OH str)

δ_H ($CDCl_3$; free base):
1.65 (2H; d, ^2J 13.5Hz; eq C3-H and C5-H), 2.08 (2H; t x d, ^2J 13.5, ^3J 13.5, 4Hz; ax C3-H and C5-H), 2.18 (3H; s; N-CH_3), 2.45 (2H; t x d, ^2J 10.7, ^3J 10.7, 1.7Hz; ax C2-H and C6-H), 2.60 (2H; d, ^2J 10.7Hz; eq C2-H and C6-H), 3.70 (1H; broad s; O-H), 3.72 (3H; s; O-CH_3), 6.72-7.22 (4H; m; Aryl-H).

δ_C : see table 24, No.1

$^m/_z$: see table 25

3.4.8 4-(3-Hydroxyphenyl)-1-methylpiperidin-4-ol (155)

To a solution of 4-(3-methoxyphenyl)-1-methylpiperidin-4-ol (149; 5g) and NaH (1.66g) in anhydrous DMF (60ml), under N_2 at 25°C, was added n-propanethiol (3.77g) dropwise, and the reaction mixture refluxed for 3 hours. The product was then cooled to 0°C, quenched with iced-water, and acidified with HCl (6M). After extraction with ether (3 x 50ml), the aqueous phase was basified with $NaHCO_3$ and extracted with ethyl acetate (3 x 100ml). The ethyl acetate extract was dried ($MgSO_4$) and evaporated in vacuo to give 4-(3-hydroxyphenyl)-1-methylpiperidin-4-ol as an oil. Treatment of this oil with ethereal-HCl gave the hydrochloride (0.45g; 8%), m.p. 231°C (Lit.,[56] 237°C).

ν max : 3150-3300, 3400-3450 cm^{-1} (2 x OH str)

δ_C : see table 24, No.2

Found : C, 59.59; H 7.37; N, 5.99%

$C_{12}H_{18}NO_2Cl$ requires : C, 59.13; H, 7.39; N, 5.75%.

m/z : see table 25

3.4.9 4-Acetyloxy-4-(3-methoxyphenyl)-1-methylpiperidine (150)

Acetyl chloride (3.5g) was added to 4-(3-methoxyphenyl)-1-methylpiperidin-4-ol (149; 1.0g) in toluene (50ml) and the mixture heated under reflux for 3 hours. The cooled product was diluted with ether (100ml) and a solid was deposited. This solid was collected by filtration and recrystallised from isopropanol to give 4-acetyloxy-4-(3-methoxyphenyl)-1-methylpiperidine hydrochloride

(0.85g; 63%), m.p. 201°C.

ν_{max} : 1760 cm^{-1} (C=O str)

δ_H ($CDCl_3$; free base) :

2.05 (3H; s; $COC\underline{H}_3$), 2.15 (2H; d x d, ^2J 13.5, ^3J 4Hz; eq C3-$\underline{H}$ and C5-$\underline{H}$), 2.29-2.50 (4H; m; ax C2-$\underline{H}$ and C6-$\underline{H}$, ax C3-$\underline{H}$ and C5-$\underline{H}$), 2.33 (3H; s; N-$C\underline{H}_3$), 2.77 (2H; d, ^2J 10.7Hz; eq C2-$\underline{H}$ and C6-$\underline{H}$), 3.78 (3H; s; O-$C\underline{H}_3$), 6.77-7.27 (4H; m; Ar-$\underline{H}$).

δ_C : see table 24, No.3

Found : C, 60.01; H, 7.55; N, 4.46%

$C_{15}H_{22}NO_3Cl$ requires : C, 60.10; H, 7.34; N, 4.67%.

m/z : see table 25

3.4.10 4-Acetyloxy-4-(3-hydroxyphenyl)-1-methylpiperidine (159; R=$COCH_3$)

n-Butyl lithium (1.3g) in hexane was added to 3-(2-tetrahydropyranyloxy)bromobenzene(4.5g) in anhydrous tetrahydrofuran (50ml) under N_2 at -55°C. The mixture was stirred at -50°C for 2 hours and then N-methylpiperidone (2g) in dry tetrahydrofuran (30ml) was added, with stirring at -45°C, over 20 minutes. The mixture was stirred at 25°C for 30 minutes. Acetic anhydride (2.5g) in dry tetrahydrofuran (30ml) was added to the mixture, which, after being stirred for 3 hours, was poured onto ice-ammonium chloride and extracted with chloroform (3 x 100ml). The combined chloroform extracts were dried ($MgSO_4$) and evaporated in vacuo to give the

title compound as the 2-tetrahydropyranyl ether. On conversion of the crude base to the hydrochloride salt the protecting group was cleaved to yield 4-acetyloxy-4-(3-hydroxyphenyl)-1-methylpiperidine hydrochloride (2.6g; 51%), m.p. 203°C (ethanol).

ν max : 3100-3300cm^{-1} (OH str), 1755 (C=O str)

δ_H ($CDCl_3$; free base) :
2.06 (3H; s; $COCH_3$), 2.10 (2H; t x d, ^2J 13.5, ^3J 13.5, 2.2Hz; eq C3-H and C5-H), 2.36 (3H; s; N-CH_3), 2.38-2.52 (4H; m; ax C2-H and C6-H, ax C3-H and C5-H), 2.81 (2H; d, ^2J 12.3Hz; eq C2-H and C6-H), 6.71-7.26 (4H; m; Aryl-H).

δ_C : see table 24, No.4

Found : C, 58.80; H, 7.09; N, 5.02%
$C_{14}H_{20}NO_3Cl$ requires : C, 58.84; H, 7.00; N, 4.90%

$^m/_z$: see table 25

3.4.11 4-(3-Hydroxyphenyl)-1-methyl-4-propionyloxypiperidine (159; R=COC_2H_5)

The reaction mixture from n-butyl lithium (1.3g), 3-(2-tetrahydropyranyloxy)bromobenzene (4.5g) and N-methylpiperidone (2g) in dry tetrahydrofuran (100ml) was decomposed with a solution of propionic anhydride (2.5g) in dry tetrahydrofuran (30ml) as outlined in section 3.4.10. The mixture was poured onto ice-ammonium chloride and extracted with chloroform (3 x 100ml). The

combined chloroform extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give the title compound as the 2-tetrahydropyranyl ether. On conversion of the crude base to the hydrochloride salt the protecting group was cleaved to yield 4-(3-hydroxyphenyl)-1-methyl-4-propionyloxypiperidine hydrochloride (3.2g; 60%), m.p. 204°C (Lit.,[57] 205-206°).

ν max : 3200-3350 cm^{-1} (OH str), 1760 cm^{-1} (C=O str)

δ_H ($CDCl_3$; free base) :
1.11 (3H; t, ^3J 7.2Hz; $CH_2\underline{CH_3}$), 2.10 (2H, t, ^2J 12.4Hz, eq C3-H and C5-H), 2.30-2.50 (6H; m; $OCO\underline{CH_2}$, ax C2-H and C6-H, ax C3-H and C5-H), 2.34 (3H; s; $N\text{-}\underline{CH_3}$), 2.80 (2H; d, ^2J 11.2Hz; eq C2-H and C6-H), 6.60-7.14 (4H; m; Aryl-H).

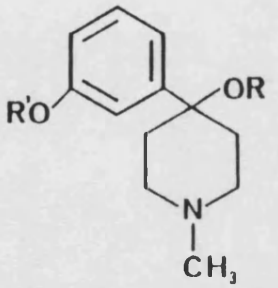
δ_C : see table 24, No.5

m/z : see table 25

3.4.12 α- and β-1,2-Dimethyl-4-propionyloxy-4-{3-tetrahydropyran-2-yloxy)phenyl}piperidine (160 and 161)

n-Butyl lithium (6.5g) in hexane was added to 3-(2-tetrahydropyranyloxy)bromobenzene (20g) in dry tetrahydrofuran (100ml) under N_2 at -55°C over a period of 20 minutes. The mixture was stirred at -50°C for 2 hours and then 1,2-dimethyl-4-piperidone (138; 10g) in tetrahydrofuran was added dropwise with stirring at -45°C. The mixture was stirred at 25°C for 1 hour. Propionic anhydride (15g) in tetrahydrofuran (30ml) was added to the mixture,

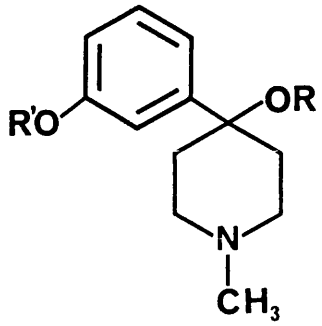
Table 24 ^{13}C-CHEMICAL SHIFTS OF PHENOLIC ANALOGUES OF REVERSED ESTERS OF PETHIDINE AND RELATED COMPOUNDS [a]



				^{13}C Chemical Shifts (ppm; TMS Internal Standard)													
No.	Compound	R	R'	N-CH$_3$	C-2 -6	C-3 -5	C-4	R			R'	Aromatic C					
								C=O	CH$_2$	CH$_3$		1'	2'	3'	4'	5'	6'
1	149	H	Me	46.25	51.63	38.27	69.97	-	-	-	55.01	150.9	110.8	159.6	112.1	129.2	117.1
2	155	H	H	45.41	50.79	37.37	68.92	-	-	-	-	150.4	111.6		112.8	128.2	115.0
3	150	COCH$_3$	Me	46.02	51.46	35.63	79.70	169.4	-	22.10	53.10	146.1	111.1	159.6	111.9	129.4	116.9
4	159 R=COCH$_3$	COCH$_3$	H	45.77	51.25	35.10	79.73	169.9	-	22.12	-	145.6	112.1	156.9	114.8	129.7	115.7
5	159 R=COC$_2$H$_5$	COCH$_2$CH$_3$	H	45.70	51.21	34.99	79.30	173.1	28.61	9.21	-	145.6	112.1	157.1	114.8	129.5	115.6

a. Spectra recorded as base in CDCl$_3$.

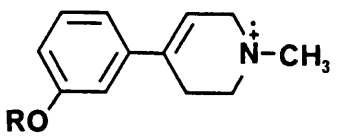
Table 25 PERCENT ABUNDANCE OF DIAGNOSTIC FRAGMENT IONS OF PHENOLIC ANALOGUES OF REVERSED ESTERS OF PETHIDINE AND RELATED COMPOUNDS



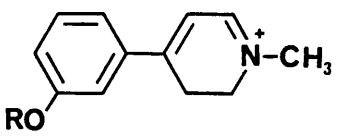
				Ion Type [a]						
No.	Compound	R	R'	M^+	A	B	C	D	E	Other
1	149	H	Me	52	12	10	15	100	61	
2	155	H	H	63	22	17	16	100	60	M^+-1 (28)
3	150	$COCH_3$	Me	4	100	39	32	22	-	CH_3CO^+ (13) CH_2CO^+ (25)
4	159; R=$COCH_3$	$COCH_3$	H	3	100	62	58	32	-	CH_3CO^+ (80) CH_2CO^+ (42)
5	159; R=COC_2H_5	$COCH_2CH_3$	H	5	80	37	100	27	-	$C_2H_5^+$ (37) $C_2H_5CO^+$ (30)

a. Ion Types

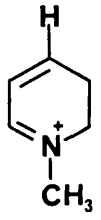
A



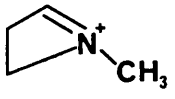
B



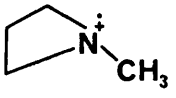
C



D



E



which, after being stirred for 3 hours, was flooded with ether. A solid was precipitated which was collected by filtration. This solid was dissolved in absolute ethanol and anhydrous ether added until solid ceased to be deposited. This solid was filtered off (shown to be mainly inorganic material) and the ethanol removed to yield a light brown solid. This solid was recrystallised from acetone to yield pure β-1,2-dimethyl-4-propionyloxy-4-{3-(tetrahydropyran-2-yloxy)phenyl}piperidine as the propionate salt (6.4g; 19%), m.p. 270°C.

ν max : 1740 cm^{-1} (C=O str)

δ_H ($CDCl_3$; free base) :
1.12 (6H; m; $CH_2C\underline{H}_3$, C2-$C\underline{H}_3$), 2.32 (3H; s; N-$C\underline{H}_3$), 1.63-2.56 (14H; m; C2-$\underline{H}$, C3-$\underline{H}$, C5-$\underline{H}$, eq C6-$\underline{H}$, $COC\underline{H}_2CH_3$, OCH_2-$C\underline{H}_2C\underline{H}_2C\underline{H}_2$-CH), 2.77 (2H; d; ax 6-$\underline{H}$), 3.60 (1H; m; O-$C\underline{H}_2$-$CH_2$), 3.90 (1H; m; O-$C\underline{H}_2$-$CH_2$), 5.38 (1H; m; O-$C\underline{H}$-O), 6.93-7.27 (4H; m; Aryl-$\underline{H}$).

δ_C : see figure 11, No.ii

Found : C, 66.29; H, 8.30; N, 2.89%
$C_{24}H_{37}NO_6$ requires : C, 66.21; H, 8.51; N, 3.22%

m/z : see table 27

The original mother liquors were reduced in volume in vacuo and then poured onto a mixture of ice and ammonia. This mixture was extracted with ether (3 x 100ml), the ether dried ($MgSO_4$) and

evaporated in vacuo to yield crude α-1,2-dimethyl-4-propionyloxy-4-{3-(tetrahydropyran-2-yloxy)phenyl}piperidine with some traces of the β- base. Fractional recrystallisation from petroleum spirit (b.p. 60-80°C) afforded the pure α-isomer (4.1g; 15%), m.p. 128°C.

ν max : 1750 cm^{-1} (C=O str)

δ_H ($CDCl_3$; free base) :
1.00 (3H; t, ^3J 7Hz; CH_3-CH_2), 1.11 (3H; d, ^3J 6Hz; C2-CH_3), 2.17 (2H; q, ^3J 7Hz; CH_2CO), 1.49-2.29 (10H; m; O-CH_2-CH_2-CH_2-CH_2-CH; C3-H, C5-H), 2.81 (3H; m; C2-H, C6-H), 3.58 (1H; m; O-CH_2-CH_2), 3.81 (1H; m; O-CH_2-CH_2), 5.37 (1H; m; O-CH-O), 6.96-7.28 (4H; m; Aryl-H).

δ_C : see figure 11, No.i

Found : C, 69.63; H, 8.79.N, 4.20%
$C_{21}H_{31}NO_4$ requires : C, 69.80; H, 8.58; N, 3.87%

m/z : see table 27

3.4.13 α-1,2-Dimethyl-4-(3-hydroxyphenyl)-4-propionyloxypiperidine (136)

To an ethanolic solution of α-1,2-dimethyl-4-propionyloxy-4-{3-(tetrahydropyran-2-yloxy)phenyl}piperidine (160; 4g) was added an excess of ethanolic-HCl. The ethanol was removed in vacuo and the residue recrystallised from acetone to yield α-1,2-dimethyl-4-(3-hydroxyphenyl)-4-propionyloxypiperidine hydrochloride as a white

hygroscopic solid (0.62g; 18%), m.p. 165°C.

δ_H : see table 26

δ_C : see figure 11, No.iii

Found : C, 58.37; H, 7.42; N, 3.98%.

$C_{16}H_{24}NO_3Cl.H_2O$ requires : C, 57.92; H, 7.84; N, 4.22%.

m/z : see table 27

3.4.14 β-1,2-Dimethyl-4-(3-hydroxyphenyl)-4-propionyloxypiperidine (137)

To an ethanolic solution of β-1,2-dimethyl-4-propionyloxy-4-{3-(tetrahydropyran-2-yloxy)phenyl}piperidine (161; 4g) was added an excess of ethanolic-HCl. The ethanol was removed in vacuo and the residue recrystallised from acetone to yield β-1,2-dimethyl-4-(3-hydroxyphenyl)-4-propionyloxypiperidine hydrochloride as a white crystalline material (0.8g; 23%), m.p. 264°C.

δ_H : see table 26

δ_C : see figure 11, No.iv

Found : C, 61.02; H, 7.72; N, 4.18%

$C_{16}H_{24}NO_3Cl$ requires : C, 61.24; H, 7.66; N, 4.46%

m/z : see table 27

Table 26 ^{1}H-N.M.R. CHARACTERISTICS OF α- AND β-2-METHYL PHENOLIC ANALOGUES OF THE REVERSED ESTER OF PETHIDINE [a]

	(136) in $CDCl_3$	(136) HCl in D_2O [d]	(137) in $CDCl_3$	(137) HCl in D_2O
N-CH_3	δ2.28, s	δ2.77, s (δ2.81, s)	δ2.29, s	δ2.89, s
C2-CH_3	δ1.16, d J6.4	δ1.37, d, J6.4 (δ1.44, d, J6.4)	δ1.09, d J6	δ1.37, d J6
2-H	δ2.29 [k]	δ3.25, m [f] (δ3.8, m) [f]	h	δ3.55 [i]
ax 3H	δ2.03 ^{2}J14.3, ^{3}J11.4	g	δ1.73 ^{2}J14.3, ^{3}J11.4	δ2.05, ^{2}J17, ^{3}J12
eq 3H	δ2.76 [c]	g	h	δ2.72 ^{2}J17, ^{3}J2
ax 5H	b	g	δ2.01 ^{2}J15.7, ^{3}J15.7, 4.3	δ2.25 ^{2}J15.7, ^{3}J14.3, 4.3
eq 5H	b	g	h	j
ax 6H	b	g	h	δ3.40 ^{2}J12.8, ^{3}J12.8, 2
eq 6H	b	g	δ2.78 ^{2}J11.4, ^{3}J2	δ3.50 ^{2}J12.8, ^{3}J2
OCOCH_2	δ2.19, q J7.1	δ2.24, q, J7.1 (δ2.37, q, J7.1)	δ2.30, q, J7	δ2.41, q J7.3
CH_2CH_3	δ1.00, t J7.1	δ0.89, t, J7.1 (δ0.98, t, J7.1)	δ1.05, t, J7	δ1.01, t J7.3
Aryl-H	δ6.67, 6.95 [e] 7.17, 7.26	δ6.85, 6.99 [e] 7.10, 7.26	δ6.56, 6.72 [e] 7.05, 7.19	δ6.81, 6.95, 7.26

Notes for Table 26

a. Spectra recorded on a JEOL GX400MHz FT N.M.R. Spectrometer.

b. Signals part of complex unresolved multiplets.

c. Eq 3H signal at approx δ2.76 as irradiation of ax 3H (δ2.03) caused broad doublet to reduce to broad singlet.

d. Values in parentheses refer to minor epimer.

e. Each signal of 1 proton intensity.

f. Irradiation of these signals caused C2-Me doublet to reduce to singlet.

g. Signals part of complex unresolved multiplets.

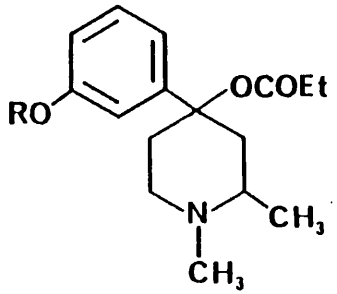
h. Unresolved signals.

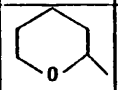
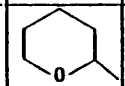
i. Signal poorly resolved, overlapped by eq 6H.

j. Poorly resolved, part of signal at δ2.72.

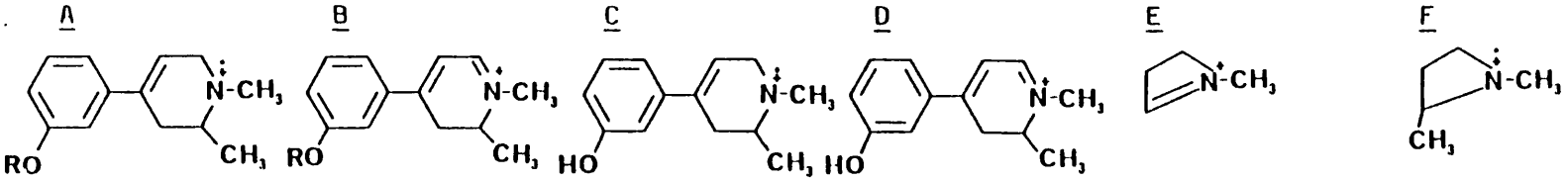
k. Poorly resolved, irradiation of C2-Me doublet (δ1.16), δ2.29 affected.

Table 27 PERCENT ABUNDANCE OF DIAGNOSTIC FRAGMENT IONS OF PHENOLIC 2-METHYL ANALOGUES OF REVERSED ESTERS OF PETHIDINE AND RELATED COMPOUNDS



				Ion Types [a]							
No.	Compound	Isomer Designation	R	$M^{\ddagger}$	A	B	C	D	E	F	Other
1	160	α		Not Seen	23	10	48	35	100	60	
2	161	β		2	50	25	100	70	58	86	
3	136	α	H	Not Seen			27	63	31	22	$C_2H_5CO^+$ (100)
4	137	β	H	Not Seen			33	69	33	18	$C_2H_5CO^+$ (100)

a. Ion Types



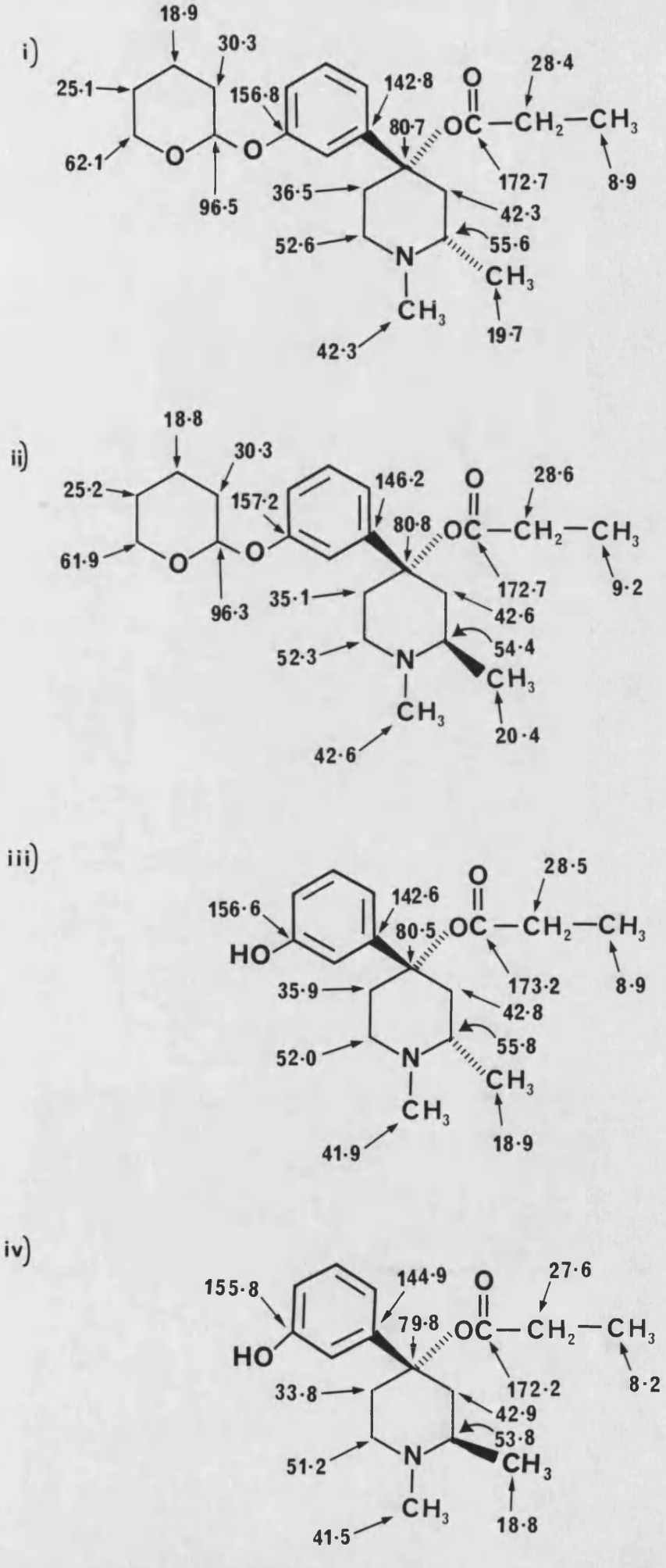


Figure 11

^{13}C-n.m.r. data for compounds (160), (161) (136) and (137)

4. REFERENCES

4. REFERENCES

1. Gulland, J.M. and Robinson, R. (1925). Mem. Proc. Manch. Lit. Phil. Soc., 69, 79; Chem. Abstr. (1926). 20, 765.

2. Gulland, J.M. and Robinson, R. (1923). J. Chem. Soc., 123, 980.

3. Gates, M. and Tschudi, G. (1952). J. Am. Chem. Soc., 74, 1109.

4. Clark, R.L., Pessolano, A.A., Weijlard, J. and Pfister, K.P. (1953). J. Am. Chem. Soc., 75, 4963.

5. Hart, E.R. and McCawley, E.L. (1944). J. Pharmacol. Exp. Ther., 82, 339.

6. Woods, L.A. (1956). Pharmacol. Rev., 8, 175.

7. Martin, W.R. (1967). Pharmacol. Rev., 19, 463.

8. Lowenstein, M.J. (1964). UK Patent 955,493.

9. Bentley, K.W. and Hardy, D.G. (1967), J.Am. Chem. Soc., 89, 3267.

10. Blane, G.F., Boura, A.L.A., Fitzgerald, A.E. and Lister, R.E. (1967). Brit. J. Pharmacol. Chemother., 30, 11.

11. Grewe, R. (1946). Naturwissenschaften, 33, 333.

12. Grewe, R. and Mondon, A. (1948). Chem. Ber., 81, 279; Chem. Abstr. (1949). 43, 4279b.

13. Isbell, H. and Fraser, H.F. (1953) J. Pharmacol. Exp. Ther., 107, 524.

14. Schnider, O. and Grussner, A. (1951). Helv. Chim. Acta., 34, 2211; Chem. Abstr. (1952). 46, 8663h.

15. Fromherz, K. and Pellmont, B. (1952). Experimentia, 8, 394; Chem. Abstr. (1953). 47, 2875e.

16. May, E.L. and Murphy, J.G. (1955). J. Org. Chem., 20, 257.

17. Ager, J.H., Jacobson, A.E. and May, E.L. (1969). J. Med. Chem., 12, 288.

18. May, E.L. and Eddy, N.B. (1959). J. Org. Chem., 24, 295.

19. Fraser, H.F. and Rosenberg, D.E. (1964). J. Pharmacol. Exp. Ther., 143, 149.

20. Beaver, W.T., Wallenstein, S.L., Houde, R.W. and Rogers, A. (1966). Clin. Pharmacol. Ther., 7, 740.

21. Eisleb, O. and Schaumann, O. (1939). Dtsch. Med. Wochenschr., 65, 967; Chem. Abstr. (1939). 33, 9442e.

22. Bockmuhl, M. and Ehrart, G. (1948). Ann., 361, 52; Chem. Abstr. (1949). 43, 4243a

23. Denton, J.E. and Beecher, H.K. (1949). J. Am. Med. Assoc., 141, 1146.

24. Freedman, A.M., Fink, M., Sharoff, R. and Zaks, A. (1967). J. Am. Med. Assoc., 202, 191.

25. Janssen, P.A.J. (1960). Synthetic Analgesics, Part I, Diphenylpropylamines, Perganon, New York.

26. Keats, A.S. and Beecher, H.K. (1952). J. Pharmacol. Exp. Ther., 105, 109.

27. Ofner, P., Walton, E., Green, A.F. and White, A.C. (1950). J. Chem. Soc., 2158.

28. Lasagna, L. and Beecher, H.K. (1954). J. Pharmacol. Exp. Ther., 112, 306.

29. Casy, A.F. (1978). Prog. Drug. Res., 22, 150.

30. Martindale: The Extra Pharmacopoeia 28th edition. p.1026, The Pharmaceutical Press, London (1982).

31. Perrine, T.D. and Eddy, N.B. (1956). J. Org. Chem., 21, 125.

32. Weiljard, J., Orahovats, P.D., Sullivan, H.R., Purdue, G., Heath, F.K. and Pfister 3rd, K. (1956). J.Am. Chem. Soc., 78, 2342.

33. Elperm, B., Gardner., L.N. and Grumbach, L. (1957). J. Am. Chem. Soc., 79, 1951.

34. Kriesel, D.C. and Gisvold, O. (1971). J. Pharm. Sci., 60, 1250.

35. Janssen, P.A.J., Jageneau, A.H.M., Demoen, P.J.A., Van De Westeringh, C., Raeymaekers, A.H.M., Wouters, M.S.J., Sanczuk, S., Hermans, B.K.F. and Loomans, J.L.M. (1959). J. Med. Pharm. Chem., 1, 105.

36. Janssen, P.A.J., Jageneau, A.H.M., Demoen, P.J.A., Van De Westeringh, C., De Canniere, J.H.M., Raeymaekers, A.H.M., Wouters, M.S.J., Sanczuk, S. and Hermans, B.K.F. (1960). J. Med. Pharm. Chem., 2, 271.

37. Eddy, N.B., Halbach, H. and Braenden, O.J. (1957). Bull. World. Hlth. Org., 17, 569.

38. Keats, A.S., Telford, J. and Kuroso, Y. (1957). Anesthesiol., 18, 690; Chem. Abstr. (1958). 52, 9447d.

39. Dekornfield, T.J. and Lasagna, L. (1960). J. Chron. Dis., 12, 252.

40. Casy, A.F., Simmonds, A.B. and Staniforth, D. (1948). J. Pharm. Pharmacol., 20, 768.

41. Langbein, A., Merz, H., Stockhus, K. and Wick, H. (1974). Narcotic Antagonists, (Eds. Brande, M.C., Harris, L.S., May, E.L., Smith, J.P. and Villareal, J.E.), Raven Press, New York, p157.

42. Bergel, F. and Morrison, A.L. (1948). Quart. Rev., 2, 349.

43. Janssen, P.A.J. and Eddy, N.B. (1960). J. Med. Pharm. Chem., 2, 31.

44. Jensen, K.A., Lindquist, F., Rekling, E. and Wolffbrandt, C.G. (1943). Dansk Tidsskr Farm., 17, 173.

45. Carabateas, P.M. and Grumbach, L. (1962). J. Med. Pharm. Chem, 5, 913.

46. Avison, A.W.D. and Morrison, A.L. (1950). J. Chem Soc., 1469.

47. Casy, A.F., Beckett, A.H., Hall, G.H. and Vallance, D.K. (1961) J. Med. Pharm. Chem., 4, 535.

48. Waters, J.A. (1977). J. Med. Chem., 20, 1496.

49. Waters, J.A. (1978). J. Med. Chem., 21, 628.

50. Beckett, A.H., Casy, A.F. and Phillips, P.M. (1960). J. Med. Pharm. Chem., 2, 245.

51. Harper, N.J. and Fullerton, S.E. (1961). J. Med. Pharm. Chem., 4, 297.

52. Razzak, K.S.A. and Hamid, K.A. (1980). J. Pharm. Sci., 69, 796.

53. Beckett, A.H., Casy, A.F. and Kirk, G. (1959). J. Med. Pharm. Chem., 1, 37.

54. Casy, A.F. and Armstrong, N.A. (1965). J. Med. Chem., 8, 57.

55. Casy, A.F., Beckett, A.H. and Armstrong, N.A. (1961). Tetrahedron, 16, 85.

56. Portoghese, P.S., Alreja, B.D. and Larson, D.L. (1981) J. Med. Chem., 24, 782.

57. Casy, A.F. and Ogungbamila, F.O. (1985). J. Pharm. Pharmacol., 37, 121.

58. Braenden, O.J., Eddy, N.B. and Halbach, H. (1955). Bull. World. Hlth. Org., 13, 937.

59. Randall, L.O. and Lehmann, G. (1948). J. Pharmacol Exp. Ther., 93, 314.

60. Ziering, A. and Lee, J. (1947). J. Org. Chem., 12, 911.

61. A.F. Casy in Guide to Molecular Pharmacology and Toxicology, Prt I (R.M. Featherstone, ed), p217 Marcel Dekker, New York. 1973.

62. Kartha, G., Ahmed, F.R. and Barnes, W.H. (1960) Acta. Crystallogr., B 525.

63. Casy, A.F. (1966). Tetrahedron, 22, 2711.

64. Casy, A.F. (1968). J. Med. Chem., 11, 188.

65. Casy, A.F., Iorio, M.A. and Podo, F. (1981) J. Org. Mag. Reson., 15, 275.

66. Jones, A.J., Casy, A.F. and McErlane, K.M.J. (1973). Can. J. Chem., 51, 1782.

67. Iorio, M.A., Casy, A.F. and May, E.L. (1975). Eur. J. Med. Chem., 10, 178.

68. Iorio, M.A. and Klee, W.A. (1977). J. Med. Chem., 20, 309.

69. Larson, D.L. and Portoghese, P.S. (1973). J. Med. Chem., 16, 195.

70. Hirschmann, H. and Hanson, K.R. (1972). J. Org. Chem., 37, 2784.

71. I.U.P.A.C. (1970). J. Org. Chem., 35, 2849.

72. Bell, K.H. and Portoghese, P.S. (1973). J. Med. Chem., 16, 589.

73. Bell, K.H. and Portoghese, P.S. (1974). J. Med. Chem., 17, 129.

74. Harper, N.J., Beckett, A.H. and Balon, A.D.J. (1960). J. Chem. Soc. Prt II, 2704.

75. Casy, A.F. and McErlane, K.M.J. (1972). J. Chem. Soc. Perkin Trans. 1, 726.

76. Hayakawa, K. and James, M.N.G. (1973) Can. J. Chem., 51, 1535.

77. Casy, A.F., Coates, J.E. and Rostron, C. (1976) J. Pharm. Pharmacol., 28, 106.

78. Nazarov, I.N. and Rudenko, V.A. (1948). Bull. Acad. Sci. USSR, 610; Chem. Abstr., (1949). 43, 2958h.

79. Shvetsov, N.I. and Kucherov, V.F. (1959). Proc. Acad. Sci. USSR, 129, 451; Chem. Abstr. (1959). 53, 21946b.

80. Nazarov, I.N., Prostakov, N.S. and Shvetsov, N.I. (1956). J. Gen. Chem. USSR, 26, 3117.

81. Jones, A.J., Casy, A.F. and McErlane, K.M.J. (1973). J. Chem. Soc. Perkin Trans. I, 2576.

82. Casy, A.F. and McErlane, K.M.J. (1972). J. Chem. Soc., Perkin Trans. 1, 334.

83. Jones, A.J., Beeman, C.P., Casy, A.F. and McErlane, K.M.J. (1973). Can. J. Chem., 51, 1790.

84. De Camp, W.H. and Ahmed, F.R. (1972). Acta. Crystallogr., B 28, 3484.

85. Nazarov, I.N. and Izbramye Tudy. (1961). Akad. Nauk. SSSR, 588; Chem. Abstr., (1962). 56, 8682c.

86. Mastryukov, E.A. and Shvetsov, N.I. (1961). Bull. Acad. Sci. USSR, 268.

87. Casy, A.F. and Ogungbamila, F.O. (1982). J. Chem. Soc. Perkin Trans. I, 749.

88. Cygler, M., Ahmed, F.R., Casy, A.F. and Ogungbamila, F.O. (August 1981). Communication to XIIth Congress and General Assembly, International Union of Crystallography, Ottowa, Canada.

89. Sorokin, O.I. (1961). Izv. Akad. Nauk. SSSR, 460; Chem. Abstr. (1961). 55, 22310d.

90. Portoghese, P.S., Gomaa, Z.S.D., Larson, D.L. and Shefter, E. (1973). J. Med. Chem., 16, 199.

91. Fries, D.S., Dodge, R.P., Hope, H. and Portoghese, P.S. (1982). J. Med. Chem., 25, 9.

92. Fries, D.S. and Portoghese, P.S. (1974). J. Med. Chem., 17, 990

93. Fries, D.S. and Portoghese, P.S. (1976). J. Med. Chem., 19, 1155.

94. Casy, A.F. (1982). Med. Research Reviews, 2, 167.

95. Casy, A.F. and Rostron, C., unpublished results.

96. Beckett, A.H. and Casy, A.F. (1954). J. Pharm. Pharmacol., 6, 986.

97. Bell, M.R. and Archer, S. (1960). J. Am Chem.Soc., 82, 4638.

98. Cignarella, G., Gallo, G.G. and Testa, E. (1961). J. Am. Chem. Soc., 83, 4999.

99. Daum, S.J., Martini, C.M., Kullnig, R.K. and Clarke, R.L. (1975). J. Med. Chem., 18, 496.

100. Blackman, S.W. and Baltzly, R. (1961). J. Am. Chem. Soc., 26, 2750.

101. Hell, C. (1881). Ber, 14, 891; J. Chem. Soc. Abstr. (1881). 40, 711.

102. Zelinsky, N. (1887). Ber., 20, 20; J. Chem. Soc. Abstr. (1887). A, 912.

103. Volhard, J. (1887). Ann., 242, 141; J. Chem. Soc. Abstr. (1888). A, 129.

104. Sonntag, N.O.V. (1953). Chem. Rev., 52, 361.

105. Harwood, H.J. (1962). Chem. Rev., 62, 99.

106. Kwart, H. and Scalzi, F.V. (1964). J. Am. Chem. Soc., 86, 5496.

107. Gaylord in 'Reduction with Complex Metal Hydrides', Interscience Publishers Inc., New York (1956).

108. Albertson, N.F. (1965). US Patent 3,202,675.

109. Cignarella, G. and Nathansohn, G.G. (1960). Gazz. Chim. Ital., 90, 1495.

110. Finklestein, H. (1910). Ber., 43, 1528; J. Chem. Soc. Abstr., (1910). AI, 453.

111. Geissman in 'Principles of Organic Chemistry' (Pauling, L., ed) p.140, W.H. Freeman and Company, London, 1968.

112. Booth, H. (1964). Tetrahedron, 20, 2211.

113. Casy, A.F., Wu, E.S.C. and Whelton, B.D. (1972). Can. J. Chem., 50, 3998.

114. Karplus, M. (1959). J. Chem. Phys., 30, 11.

115. Sternhell, S. (1969). Quart. Rev., 23, 236.

116. Chen, C.Y. and Le Fevre, R.J.W. (1965). J. Chem. Soc., 3473.

117. Schenk, H., MacGillavry, C.H., Skolnik, S. and Laan, J. (1967). Acta Cryst., 23, 423.

118. Pauling, P. and Petcher, T.J. (1969). Chem. Commun., 1001.

119. Casy, A.F. and Jeffery, W.K. (1972). Can. J. Chem., 50, 803.

120. Bishop, R.J., Fodor, G., Katritzky, A.R., Soti, F., Sutton, L.E. and Swinbourne, F.J. (1966). J. Chem. Soc. (C), 74.

121. Cope, A.C. and D'Addieco, A.A. (1951). J. Am. Chem. Soc., 73, 3419.

122. Casy, A.F. and Coates, J.E. (1974). J. Org. Mag. Reson., 6, 441.

123. Bell, M.R. and Archer, S. (1960). J. Am. Chem. Soc., 82, 151.

124. Supple, J.H., Prigden, L.N. and Kaminski, J.J. (1969). Tetrahedron Lett., 1829.

125. Casy, A.F., Chatten, L.G. and Khullar, K.K. (1969). J. Chem. Soc. (C), 2491.

126. Karabatsos, G.J., Sonnichsen, G.C., Hsi, N. and Fenoglio, D.J. (1967). J. Am. Chem,. Soc., 89, 5067.

127. Johnson, C.E. and Bovey, F.A. (1958). J. Chem. Phys., 29, 1012.

128. Allinger, N.L. and Tribble, H.T. (1971). Tetrahedron Lett., 3259.

129. Foster, R. and Ing, H.R. (1956). J. Chem. Soc., 1, 938.

130. Pople, J.A., Schneider, W.G. and Bernstein, H.J. (1959). High Resolution Nuclear Magnetic Resonance, McGraw-Hill, New York.

131. Hanisch, P., Jones, A.J., Casy, A.F. and Coates, J.E. (1977). J. Chem. Soc. Perkin II, 1202.

132. Casy, A.F., Chatten, L.G. and Khullar, K.K. (1970). Can. J. Chem., 48, 2372.

133. McErlane, K.M.J. and Casy, A.F. (1972). J. Chem. Soc. Perkin I, 339.

134. Beckmann, E. (1886). Ber., 19, 988.

135. Donaruma, G. and Heidt, W.Z. (1960). Org. Reactions, 11, 1.

136. Benton, F.L. and Dillon, T.E. (1942). J. Am. Chem. Soc., 64, 1128.

137. Underwood, H.W. and Toone, G.C. (1930). J. Am. Chem. Soc., 52, 391.

138. Wiberg, E. and Sutterlin, W. (1931). Z. Anorg. Allgem. Chem., 202, 22.

139. Wiberg, E. and Sutterlin, W. (1931). Z. Anorg. Allgem. Chem., 202, 37.

140. Rice, K.C. (1977). J. Med. Chem., 20, 164

141. Montzka, T.A., Matiskella, J.D. and Partyka, R.A. (1974). Tetrahedron Lett., 1325.

142. Kraiss, G. and Nador, K. (1971). Tetrahedron Lett., 57.

143. Hobson, J.D. and McCluskey, J.G. (1967). J. Chem. Soc., 2015.

144. Kung, F.E. (1945). US Patent 2,377,085.

145. Olofson, R.A., Schnur, R.C., Bunes, L. and Pepe, J.P. (1977). Tetrahedron Lett., 1567.

146. Streitwieser Jr, A. (1956). Chem. Rev., 56, 571.

147. DeWolfe, R.H. and Young, W.G. (1956). Chem. Rev., 56, 769.

148. Michael, A. (1887). J. Prakt. Chem., 35, 349.

149. Bergmann, E. (1959). Org. Reactions, 10, 179.

150. Baggs, M.E.M. and Gregory, B. (1980). Can. J. Chem., 58, 794.

151. Mannich, C. and Krosche, W. (1912). Arch. Pharm., 250, 647; J. Chem. Soc. Abstr., (1913), 104, 101.

152. Cope, A.C. and Trumbull, E.R. (1960). Org. Reactions, 11, 317.

153. Mertes, M.P., Hanna, P.E., Ramsey, A.A. (1970). J. Med. Chem., 13, 125.

154. Ziering, A., Motchane, A. and Lee, J. (1957). J. Org. Chem., 22, 1521.

155. Beckett, A.H., Lingard, R.G. and Theobald, A.E.E. (1969). J. Med. Chem., 12, 563.

156. Casy, A.F., Beckett, A.H., lorio, M.A. and Youssef, H.Z. (1965). Tetrahedron, 21, 3387.

157. Brewster, J.H. (1954). J. Am. Chem. Soc., 76, 6361.

158. Boudart, M. (1952). J. Am. Chem. Soc., 74, 3556.

159. Linstead, R.P., Doering, W.E., Davis, S.B., Levine, P. and Whetstone, R.R. (1942). J. Am. Chem. Soc., 64, 1985.

160. Willstatter, R., Seltz, F. and Bumm, E. (1928). Ber., 61, 871; British Chem. Abstr., (1928), A, 756.

161. Burton, H. and Ingold, C.K. (1929). J. Chem. Soc., 2022.

162. Waldeland, C.R., Zartman, W. and Adkins, H. (1933). J. Am. Chem. Soc., 55, 4234.

163. Archer, S. (1964). US Patent 3,133,073; Chem. Abstr., 61, 8356g.

164. Garbisch, E.W. (1967). Chem. Commun., 806.

165. Mitsui, S., Kudo, Y. and Kobayashi, M. (1969). Tetrahedron, 25, 1921.

166. Hanotier, J., Camerman, Ph., Hanotier-Bridoux, M. and de Radzitzky, P. (1972). J. Chem. Soc. Perkin Trans. 2, 2247.

167. Nishimura, T. (1963). Org. Synth, Coll. Vol. IV, p713.

168. Bryant, D.R., Mckeon, J.E. and Ream, B.C. (1968). Tetrahedron Lett., 3371.

169. Bryant, D.R., Mckeon, J.E. and Ream, B.C. (1969). J. Org. Chem., 34, 1106.

170. Bryant, D.R., McKeon, J.E. and Ream. B.C. (1968). J. Org. Chem., 33, 4123.

171. Andrulis, P.J., Dewar, M.J.S., Dietz, R. and Hunt, R.L. (1966). J. Am. Chem. Soc., 88, 5473.

172. Kochi, J.K. in 'Organometallic Mechanisms and Catalysis' Academic Press, New York, 1978.

173. Becker, Y. and Stille, J.K. (1978). J. Am. Chem. Soc., 100, 838.

174. Schaefer, J.P. and Bloomfield, J.J. (1967). Org. Reactions, 15, 1.

175. Pasteur, I., in Lecons de Chimie Professees en 1860, Paris (1861); Researches on the Molecular Asymmetry of Natural Organic Products, Alembic Club Reprints, No.14, Edinburgh (1905).

176. Amiard, G. (1956). Bull. Soc. Chim. Fr., 447; Chem. Abstr., (1956), 50, 8789f.

177. Pasteur, L. (1858). Compt. rend., 46, 615.

178. Khorana H.G. (1953). Chem. Rev., 53, 145.

179. Feutrill, G.I. and Mirrington, R.N. (1970). Tetrahedron Lett., 16, 1327.

180. Lawson, J.A. and DeGraw, J.I. (1977). J. Med. Chem., 20, 165.

181. Lednicer, D., Von Voigtlander, P.F. and Emmert, D.E. (1981). J. Med. Chem., 24 341.

182. Dalling, D.K. and Grant, D.M. (1967). J. Am. Chem. Soc., 89, 6612.

183. Dewey, W.L., Harris, L.S., Howes, J.F. and Nuite, J.A. (1970). J. Pharmacol. Exp. Ther., 175, 435.

184. Harris, L.S. and Pierson, A.K. (1964). J. Pharmacol. Exp. Ther., 143, 141.

185. Hendershot, L.C. and Forsaith, J. (1959). J. Pharmacol. Exp. Ther., 125, 237.

186. Bentley, K.W. and Ball, J.C. (1958). J. Org. Chem., 23, 1720.

187. Andrisano, R., Angeloni, A.S., Del Moro, F. and Tramontini, M. (1965). Ann. Chim. (Rome), 55, 968; Chem. Abstr. 64, 6444f.

188. Breckpot, R. (1923). Bull. Soc. Chim. Belg., 32, 412; Chem Abstr. (1924). 18, 1114.

189. Mistryukov, E.S. and Aronova, N.I. (1966). Izv. Akad. Nauk. SSSR, 2171; Chem. Abstr. (1967). 66, 104877c.